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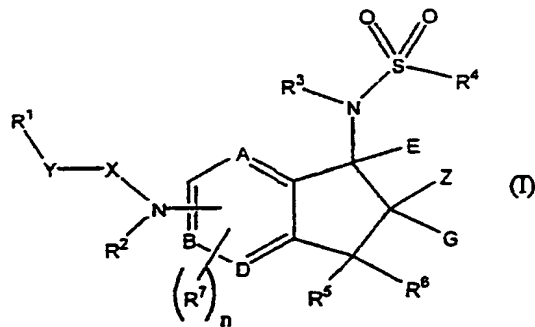
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(54) Title: POTASSIUM CHANNEL INHIBITORS



(57) Abstract: Compounds of formula (I) useful as potassium channel inhibitors and especially useful for the treatment of cardiac arrhythmias and cell proliferative disorders are described.

WO 01/46155 A1

POTASSIUM CHANNEL INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. 119 (e)(1) of prior filed provisional applications 60/231,296 filed September 8, 2000 and 60/171,397 filed on December 21, 1999.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is broadly directed to a class of compounds useful as potassium channel inhibitors.

2. Description of Related Art

The importance of potassium channels was first recognized almost fifty years ago when Hodgkin and Huxley discovered that potassium ions contributed to the current that excited the squid giant axon. Research in the area, however, was hampered by the lack of selective, high affinity ligands for potassium channels. But the advent of recombinant DNA techniques and single cell and whole cell voltage clamp techniques has changed the slow pace of the field. Indeed, potassium channels which exhibit functional, pharmacological and tissue distribution characteristics have been cloned. These cloned potassium channels are useful targets in assays for identifying candidate compounds for the treatment of various disease states. Potassium channels have turned out to be the most diverse family of ion channels discovered to date. They modulate a number of cellular events such as muscle

contraction, neuro-endocrine secretion, frequency and duration of action potentials, electrolyte homeostasis, and resting membrane potential.

Potassium channels are expressed in eukaryotic and prokaryotic cells, and are elements in the control of electrical and nonelectrical cellular functions. Potassium channels have been classified according to their biophysical and pharmacological characteristics. Subclasses of these channels have been named based on amino acid sequence and functional properties. Salient among these are the voltage dependent potassium channels, for example voltage gated potassium channels (*e.g.*, Kv1, Kv2, Kv3, Kv4). Subtypes within these subclasses have been characterized as to their putative function, pharmacology and distribution in cells and tissues (Chandy and Gutman, "Voltage-gated potassium channel genes" in Handbook of Receptors and Channels- Ligand and Voltage-gated Ion Channels, ed. R. A. North, 1995; Doupnik et al., *Curr. Opin. Neurobiol.* 5:268, 1995). For example, the Kv1 class of potassium channels is further subdivided depending on the molecular sequence of the channel, for example Kv 1.1, Kv 1.3, Kv 1.5. Functional voltage-gated K⁺ channels can exist as multimeric structures formed by the association of either identical or dissimilar subunits. This phenomenon is thought to account for the wide diversity of K⁺ channels. However, subunit compositions of native K⁺ channels and the physiologic role that particular channels play are, in most cases, still unclear.

Membrane depolarization by Kv 1.3 inhibition has been shown to be an effective method to prevent T-cell proliferation and therefore has applications in many autoimmune conditions. Inhibition of K⁺ channels in the plasma membrane of human T -lymphocytes has been postulated to play a role in eliciting immunosuppressive responses by regulating intracellular Ca⁺⁺ homeostasis, which has been found to be important in T-cell activation.

The Kv 1.3 voltage-gated potassium channel is found in neurons, blood cells, osteoclasts and T-lymphocytes. The Chandy and Cahalan laboratories proposed a

hypothesis that blocking the Kv 1.3 channel would elicit an immunosuppressant response. (Chandy *et al.*, *J. Exp. Med.* 160, 369, 1984; Decoursey *et al.*, *Nature*, 307, 465, 1984). However, the K⁺ channel blockers employed in their studies were non-selective. Until research with the peptide margatoxin, a peptide found in scorpion venom, no specific inhibitor of the Kv 1.3 channel existed to test this hypothesis. Although a laboratory (Price *et al.*, *Proc. Natl. Acad. Sci. USA*, 86, 10171, 1989) showed that charybdotoxin would block Kv 1.3 in human T cells, charybdotoxin was subsequently shown to inhibit four different K⁺ channels (Kv 1.3 and three distinct small conductance Ca⁺⁺ activated K⁺ channels) in human T-lymphocytes, limiting the use of this toxin as a probe for the physiological role of Kv 1.3 (Leonard *et al.*, *Proc. Natl. Acad. Sci. USA*, 89, 10094, 1992). Margatoxin, on the other hand, blocks only Kv 1.3 in T-cells, and has immunosuppressant activity in both *in vitro* and *in vivo* models. (Lin *et al.*, *J. Exp. Med.*, 177, 637, 1993). The therapeutic utility of this compound, however, is limited by its potent toxicity. Recently, a class of compounds has been reported that may be an attractive alternative to the above-mentioned drugs, see for example U.S. Patent Nos. 5,670,504; 5,631,282; 5,696,156; 5,679,705; and 5,696,156. While addressing some of the activity/toxicity problems of previous drugs, these compounds tend to be of large molecular weight and are generally produced by synthetic manipulation of a natural product, isolation of which is cumbersome and labor intensive.

Immunoregulatory abnormalities have been shown to exist in a wide variety of autoimmune and chronic inflammatory diseases, including systemic lupus erythematosus, chronic rheumatoid arthritis, type I and II diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis and other disorders such as Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, ichthyosis, Graves ophthalmopathy and asthma.

Although the underlying pathogenesis of each of these conditions may be quite

different, they have in common the appearance of a variety of auto-antibodies and self-reactive lymphocytes. Such self-reactivity may be due, in part, to a loss of the homeostatic controls under which the normal immune system operates. Similarly, following a bone-marrow or an organ transplantation, the host lymphocytes recognize the foreign tissue antigens and begin to produce antibodies which lead to graft rejection.

One end result of an autoimmune or a rejection process is tissue destruction caused by inflammatory cells and the mediators they release. Anti-inflammatory agents such as NSAID's act principally by blocking the effect or secretion of these mediators but do nothing to modify the immunologic basis of the disease. On the other hand, cytotoxic agents, such as cyclophosphamide, act in such a nonspecific fashion that both the normal and autoimmune responses are shut off. Indeed, patients treated with such nonspecific immunosuppressive agents are as likely to succumb from infection as they are from their autoimmune disease.

Cyclosporin A (CsA), which was approved by the US FDA in 1983 is currently the leading drug used to prevent rejection of transplanted organs. In 1993, FK-506 (Prograf) was approved by the US FDA for the prevention of rejection in liver transplantation. CsA and FK-506 act by inhibiting the body's immune system from mobilizing its vast arsenal of natural protecting agents to reject the transplant's foreign protein. In 1994, CsA was approved by the US FDA for the treatment of severe psoriasis and has been approved by European regulatory agencies for the treatment of atopic dermatitis. Though they are effective in fighting transplant rejection, CsA and FK-506 are known to cause several undesirable side effects including nephrotoxicity, neurotoxicity, and gastrointestinal discomfort. Therefore, a selective immunosuppressant without these side effects still remains to be developed. Potassium channel inhibitors promise to be the solution to this problem.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in

clinical practice and is likely to increase in prevalence with the aging of the population. Currently, AF affects more than 1 million Americans annually, represents over 5% of all admissions for cardiovascular diseases and causes more than 80,000 strokes each year in the United States. While AF is rarely a lethal arrhythmia, it is responsible for substantial morbidity and can lead to complications such as the development of congestive heart failure or thromboembolism. Currently available Class I and Class III antiarrhythmic drugs reduce the rate of recurrence of AF, but are of limited use because of a variety of potentially adverse side effects including ventricular proarrhythmia. Because current therapy is inadequate and fraught with side effects, there is a clear need to develop new therapeutic approaches.

Antiarrhythmic agents of Class III are drugs that cause a selective prolongation of the duration of the action potential without significant cardiac depression. Available drugs in this class are limited in number. Examples such as sotalol and amiodarone have been shown to possess interesting Class III properties (Singh B.N., Vaughan Williams E.M. "A Third Class Of Anti-Arrhythmic Action: Effects On Atrial And Ventricular Intracellular Potentials And Other Pharmacological Actions On Cardiac Muscle, of MJ 1999 and AH 3747" Br. *J Pharmacol* 1970; 39:675-689. and Singh B.N., Vaughan Williams E. M, "The Effect Of Amiodarone, A New Anti-Anginal Drug, On Cardiac Muscle", Br *J Pharmacol* 1970; 39:657-667.), but these are not selective Class III agents. Sotalol also possesses Class II effects which may cause cardiac depression and is contraindicated in certain susceptible patients. Amiodarone, also is not a selective Class III antiarrhythmic agent because it possesses multiple electrophysiological actions and is severely limited by side effects (Nademanee, K. "The Amiodarone Odessey". *J. Am. Coll. Cardiol.* 1992; 20:1063-065.) Drugs of this class are expected to be effective in preventing ventricular fibrillation. Selective class III agents, by definition, are not considered to cause myocardial depression or an induction of arrhythmias due to inhibition of conduction

of the action potential as seen with Class I antiarrhythmic agents.

Class III agents increase myocardial refractoriness via a prolongation of cardiac action potential duration. Theoretically, prolongation of the cardiac action potential can be achieved by enhancing inward currents (i.e. Na^+ or Ca^{2+} currents; hereinafter I_{Na} and I_{Ca} , respectively) or by reducing outward repolarizing potassium (K^+) currents. The delayed rectifier (IK) K^+ current is the main outward current involved in the overall repolarization process during the action potential plateau, whereas the transient outward (I_{to}) and inward rectifier (I_{K1}) K^+ currents are responsible for the rapid initial and terminal phases of repolarization, respectively. Cellular electrophysiologic studies have demonstrated that IK consists of two pharmacologically and kinetically distinct K^+ current subtypes, IKr (rapidly activating and deactivating) and IKs (slowly activating and deactivating) (Sanguinetti and Jurkiewicz, Two Components Of Cardiac Delayed Rectifier K^+ Current: Differential Sensitivity To Block By Class III Antiarrhythmic Agents, *J Gen Physiol* 1990, 96:195-215). Class III antiarrhythmic agents currently in development, including d-sotalol, dofetilide (UK-68,798), almokalant (H234/09), E-4031 and methanesulfonamide-N-[1'-6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl]-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl] monochloride, predominantly, if not exclusively, block IKr . Although, amiodarone is a blocker of IKs (Balser J.R. Bennett, P.B., Hondeghem, L.M. and Roden, D.M. "Suppression Of Time-Dependent Outward Current In Guinea Pig Ventricular Myocytes: Actions Of Quinidine And Amiodarone. *Circ. Res.* 1991, 69:519-529), it also blocks I_{Na} , and I_{Ca} , effects thyroid function, is a nonspecific adrenergic blocker, and acts as an inhibitor of the enzyme phospholipase (Nademanee, K. "The Amiodarone Odessey". *J. Am. Coll. Cardiol.* 1992; 20:1063-1065). Therefore, its method of treating arrhythmia is uncertain. Most Class III agents that are known to be in development predominantly block IKr .

Reentrant excitation (reentry) has been shown to be a prominent mechanism underlying supraventricular arrhythmias in man. Reentrant excitation requires a critical balance between slow conduction velocity and sufficiently brief refractory periods to allow for the initiation and maintenance of multiple reentry circuits to coexist simultaneously and sustain AF. Increasing myocardial refractoriness by prolonging action potential duration (APD), prevents and/or terminates reentrant arrhythmias. Most selective Class III antiarrhythmic agents currently in development, such as d-sotalol and dofetilide predominantly, if not exclusively, block IKr, the rapidly activating component of IK found both in atrium and ventricle in man.

Since these IKr blockers increase APD and refractoriness both in atria and ventricle without affecting conduction per se, theoretically they represent potential useful agents for the treatment of arrhythmias like AF. These agents have a liability in that they have an enhanced risk of proarrhythmia at slow heart rates. For example, torsades de points has been observed when these compounds are utilized (Roden, D.M. "Current Status of Class III Antiarrhythmic Drug Therapy", *Am J. Cardiol*, 1993; 72:44B-49B). This exaggerated effect at slow heart rates has been termed "reverse frequency-dependence", and is in contrast to frequency-independent or frequency-dependent actions (Hondeghe, L.M. "Development of Class III Antiarrhythmic Agents" *J. Cardiovasc. Cardiol.* 20 (Suppl. 2):S17-S22).

The slowly activating component of the delayed rectifier (IKs) potentially overcomes some of the limitations of IKr blockers associated with ventricular arrhythmias. Because of its slow activation kinetics however, the role of IKs in atrial repolarization may be limited due to the relatively short APD of the atrium. Consequently, although IKs blockers may provide distinct advantage in the case of ventricular arrhythmias, their ability to affect SVT is considered to be minimal.

The ultra-rapidly activating delayed rectifier K⁺ current (I_{kur}) is believed to

represent the native counterpart to a cloned potassium channel designated Kv1.5 and, while present in human atrium, it appears to be absent in human ventricle.

Furthermore, because of its rapidity of activation and limited slow inactivation, I_{kur} is believed to contribute significantly to repolarization in human atrium.

Consequently, a specific blocker of I_{kur} , that is a compound which blocks Kv 1.5, would overcome the shortcoming of other compounds by prolonging refractoriness by retarding repolarization in the human atrium without causing the delays in ventricular repolarization that underlie arrhythmogenic after depolarizations and acquired long QT syndrome observed during treatment with current Class III drugs.

In intact human atrial myocytes an ultra-rapidly activating delayed rectifier K⁺ current I_{kur} which is also known as the sustained outward current, I_{sus} or I_{so} , has been identified and this current has properties and kinetics identical to those expressed by the human K⁺ channel clone (hKv1.5, HK2) when isolated from human heart and stably expressed in human (HEK-293) cell lines. (Wang, Fermini and Natel, 1993, Circ Res 73:1061-1076; Fedida et al., 1993, Circ Res 73:210-216; Snyders, Tamkun and Bennet, 1993, J Gen Physiol 101:513-543) and originally cloned from rat brain (Swanson et al., 1990, Neuron 4:929-939). Although various antiarrhythmic agents are now available on the market, those having both satisfactory efficacy and a high margin of safety have not been obtained. For example, antiarrhythmic agents of Class I according to the classification scheme of Vaughan-Williams ("Classification Of Antiarrhythmic Drugs" In: Cardiac Arrhythmias, edited by: E. Sandoe, E. Flensted-Jensen, K. Olesen; Sweden, Astra, Sodertalje, pp449-472, 1981) which cause a selective inhibition of the maximum velocity of the upstroke of the action potential (v_{max}) are inadequate for preventing ventricular fibrillation. In addition, they have problems regarding safety, namely, they cause a depression of myocardial contractility and have a tendency to induce arrhythmias due to an inhibition of impulse conduction. Beta-adrenoceptor blockers and calcium antagonists which

belong to Class II and IV, respectively, have a defect in that their effects are either limited to a certain type of arrhythmia or are contraindicated because of their cardiac depressant properties in certain patients with cardiovascular disease. Their safety, however, is higher than that of the antiarrhythmic agents of Class I.

The present invention is related to compounds which are useful as inhibitors of potassium channel function. The compounds of the invention are especially active as inhibitors of voltage-gated potassium channels. The potassium channel inhibitors of the invention may therefore be utilized for the treatment of diseases in which prolongation of cellular action potentials would be beneficial, which include, but are not limited to, cardiac arrhythmias. In addition, compounds of the invention may be utilized for treating disorders in which induction of cell membrane depolarization would be beneficial, which include, but are not limited to, cell proliferative disorders.

WO 98/04521 (see U.S. 6,083,986) describes a class of indane potassium channel inhibitors said to be useful for treating cardiac arrhythmias and cell proliferative disorders.

It is an object of the present invention to provide compounds which are useful for the treatment of diseases in mammals, including humans, and especially for the management of diseases which can be treated by inhibiting cell membrane potassium channels, such as the potassium channels responsible for cardiac $I_{K_{ur}}$ potassium current, or the potassium channels responsible for T-lymphocyte I_{K_n} potassium current, and potassium channels containing one of Kv1.5 or Kv1.3 α -subunit gene products.

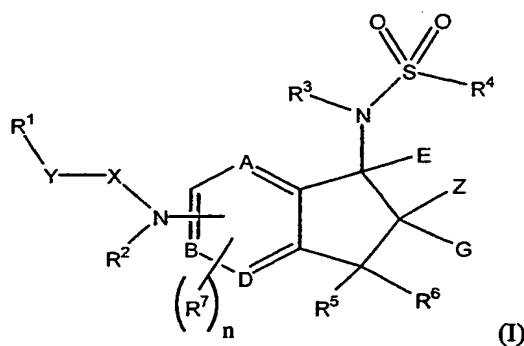
Another object of the invention is to provide a method of treating diseases in mammals, including humans, which respond to the inhibition of potassium channel function, which method comprises administering to a mammal in need thereof a compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION

This invention describes compounds and their utility as inhibitors of voltage-dependent potassium channel function, particularly potassium channels (i.e., I_{Kur} , Kv1.5) that could serve as targets for the treatment of cardiac arrhythmias especially those occurring in the atria (e.g., atrial flutter and atrial fibrillation) (Wang et al., *Circ. Res.* 73:1061, 1993; Fedida et al., *Circ. Res.* 73:210, 1993; Wang et al., *J. Pharmacol. Exp. Ther.* 272:184, 1995), as well as the potassium channels (i.e., I_{Kn} , Kv1.3) that could serve as targets for the treatment of immunologic diseases (Kaczorowski and Koo, *Perspectives in Drug Discovery and Design* 2:233, 1994). Consequently, the present invention also provides a method for treating diseases which respond to the inhibition of potassium channel function, such as cardiac arrhythmias and various immunologic diseases, using the compounds of the invention.

The invention is particularly based on our discovery that the compounds of the following formula (I) are inhibitors of potassium channel function. In particular, these compounds have demonstrated activity against the human potassium channels/currents I_{Kur} , I_{Kn} , Kv1.5, Kv1.3. As a result, these compounds are useful in the treatment of cardiac arrhythmias and cell proliferative disorders.

Thus, in a first aspect, the present invention concerns compounds having potassium channel inhibitory activity of the formula (I), or a pharmaceutically acceptable salt or prodrug thereof



wherein,

A, B, and D are selected from a substituted carbon atom, a nitrogen atom or N→O, wherein at least one of A, B, and D is a substituted carbon atom and at most only one of A, B and D is N→O;

E and G are each hydrogen or E and G taken together form a bond (site of unsaturation);

R¹ is selected from hydrogen, alkyl, carbocycloalkyl, aryl, heterocyclo, heteroaryl, alkoxy, aryloxy, and substituted amino;

Y is selected from a bond (i.e., R¹ and X are directly linked), alkyl, carbocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclo;

X is one of C=O, C=S or SO₂;

R² and R³ are independently selected from hydrogen (H), alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, (heteroaryl)alkyl, aminoalkyl; substituted aminoalkyl, carboxyalkyl, alkoxyalkanoyl, aminoalkanoyl, substituted aminoalkanoyl, alkanoylamidoalkyl, alkanoyl(substituted amido)alkyl,

aroylelamidoalkyl, aroyle(substituted amido)alkyl, heterocyclocarbonylamidoalkyl, heterocyclocarbonyl(substituted amido)alkyl, heteroaroylelamidoalkyl, and heteroaroyle(substituted amido)alkyl;

R^4 is selected from alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heteroaryl and heterocyclo;

R^5 and R^6 are each independently selected from hydrogen and alkyl;

R^7 is independently selected from hydrogen, alkyl, hydroxy, alkoxy, amino, substituted amino, nitro, cyano, halo, carboxy, alkoxycarbonyl, aminocarbonyl, substituted aminocarbonyl and n is 1, 2 or 3;

Z is selected from hydrogen, alkyl, hydroxy, SH, alkoxy, aryloxy, alkylthio, amino, substituted amino, alkoxycarbonyl, alkanoylamido, aroylelamido, heterocyclocarbonylamido, heteroaroylelamido, alkanoyl(alkylsubstituted) amido, aroyle(alkylsubstituted)amido, heteroaroyle(alkylsubstituted)amido, and heterocyclocarbonyl(alkyl substituted)amido;

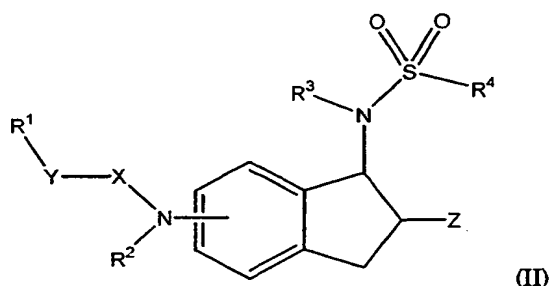
with the provisos that

i) when R^4 is aryl, then R^4 is not a 3,4-dialkoxy phenyl, or a 3-cycloalkylalkoxy, 4-alkoxy phenyl and

ii) when A, B, and D are all CH, and Z is H, OR^a , or NR^bR^c , wherein R^a is one of H, $(CH_2)_m-R^8$ or $C(O)-(CH_2)_m-R^8$, m is 1 to 5, R^8 is $N(R^9)_2$, $N(R^9)_3L$ or CO_2R^9 , each R^9 being independently selected from one of H or alkyl, and L is a counter ion, R^b is H

or alkyl; R^c is H, alkyl, or CO_2R^{10} , and R^{10} is alkyl; then when R^2 is hydrogen, or methyl, R^3 is not hydrogen, or alkyl (especially methyl), and when R^3 is H, or alkyl (especially methyl) then R^2 is not H, or methyl.

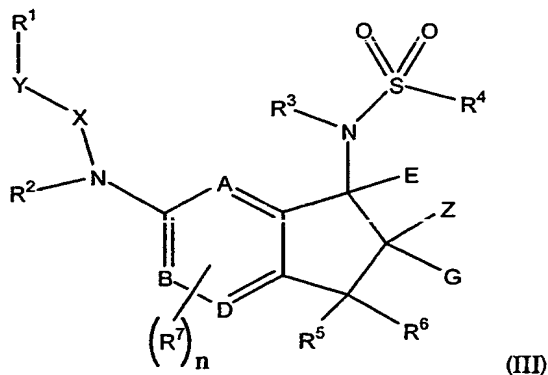
In a preferred class of compounds of formula (I), A, B and D are substituted carbon atoms, E, G, R^5 , R^6 and R^7 are each a hydrogen, Z is selected from hydrogen, alkyl, hydroxyl, amino and substituted amino and the remaining substituents and provisos are as defined above in connection with formula (I), as is represented in the following formula (II), (and again including the pharmaceutically acceptable salts or prodrugs thereof)



In a more preferred subset of compounds of formula (II) (and their pharmaceutically acceptable salts, or prodrugs), R^1 is selected from H alkyl, carbocycloalkyl, aryl, and heteroaryl; X is C=O ; Y is selected from a bond (i.e., R^1 and X are directly linked), alkyl, carbocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclo; R^2 and R^3 are independently selected from H, alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl and (heteroaryl)alkyl; R^4 is selected from aryl and heteroaryl; Z is selected from H, OH, amino and substituted amino.

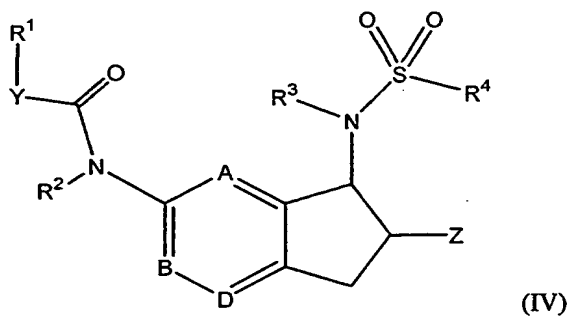
In another aspect, the present invention concerns indane compounds having

potassium channel inhibition activity of the formula (III)), or pharmaceutically acceptable salts or prodrugs thereof:



wherein all of the variables have the meaning ascribed to them in connection with formula (I) and formula (III) is subject to the same provisos as formula (I).

Yet another preferred subclass of compounds (including their pharmaceutically acceptable salts or prodrugs) falling within the compounds of formula (I) is represent by the following formula (IV):



wherein

A, B, and D are all CH, or one of A, B, and D is a nitrogen atom or N=O;

R¹ is selected from hydrogen, alkyl, carbocycloalkyl, aryl, heterocyclo, heteroaryl, alkoxy, aryloxy and substituted amino;

Y is selected from a bond, alkyl, carbocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclo;

R^2 and R^3 are independently selected from hydrogen, alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, (heteroaryl)alkyl, aminoalkyl; substituted aminoalkyl, carboxyalkyl, alkoxyalkanoyl and aminoalkanoyl;

R^4 is selected from aryl, heteroaryl and heterocyclo;

Z is selected from hydrogen, alkyl, hydroxy, SH, alkoxy, aryloxy, alkylthio, amino, substituted amino, alkoxyalkanoyl, alkanoylamido, aroylamido, heteroaroylamido, heterocyclocarbonylamido, alkanoyl(alkylsubstituted)amido, aroyl(alkylsubstituted)amido, heteroaroyl(alkylsubstituted)amido and heterocyclocarbonyl(alkylsubstituted)amido;

with the provisos that

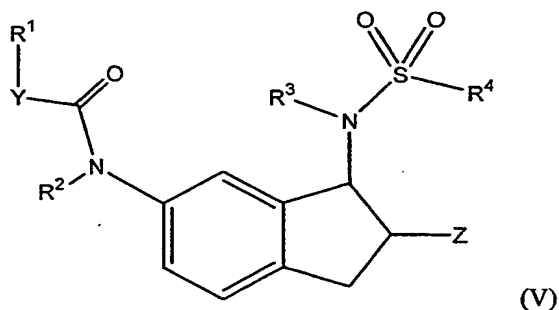
i) when R^4 is aryl, then R^4 is not a 3,4-dialkoxy phenyl, or a 3-cycloalkylalkoxy, 4-alkoxy phenyl and

ii) when A, B, and D are all CH, and Z is H, OR^a , or NR^bR^c , wherein R^a is one of H, $(CH_2)_m-R^8$ or $C(O)-(CH_2)_m-R^8$, m is 1 to 5, R^8 is $N(R^9)_2$, $N(R^9)_3L$ or CO_2R^9 , each R^9 being independently selected from one of H or alkyl, and L is a counter ion, R^b is H or alkyl; R^c is H, alkyl, or CO_2R^{10} , and R^{10} is alkyl; then when R^2 is hydrogen, or methyl, R^3 is not hydrogen, or alkyl (especially methyl), and when R^3 is H, or alkyl

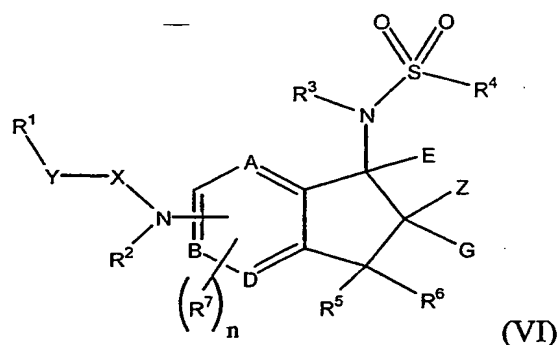
(especially methyl) then R^2 is not H, or methyl.

Preferably, R^4 in the prior embodiments is phenyl *per se* or a phenyl substituted with one or more groups in the 2 (ortho), 3 (meta), or 4 (para) positions, wherein said groups are selected from C_{1-5} alkyl, C_{1-5} alkoxy, cyano, halo and trifluoromethyl. Alternatively, R^4 is an optionally substituted heteroaryl, an optionally substituted heterocyclo or an optionally substituted carbocycloalkyl, wherein said optionally substituted moieties may be substituted with C_{1-5} alkyl, C_{1-5} alkoxy, cyano, halo and trifluoromethyl.

In a preferred class of the compounds of formula (IV) (subject to the same provisos and including pharmaceutically acceptable salts or prodrugs thereof), A, B and D are all -CH-; Z is selected from hydrogen and hydroxyl, Y is selected from a single bond, alkyl, aryl, heteroaryl and heterocyclo, R^2 is selected from aryl, aralkyl, heteroaryl and heteroaralkyl, and R^3 is selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl, and the remaining substituents are as defined above, as is represented in the following formula (V):



In other aspects, the present invention concerns compounds having potassium channel inhibitory activity of the formula (VI), or a pharmaceutically acceptable salt or prodrug thereof



wherein,

A, B, and D are selected from a substituted carbon atom, a nitrogen atom or N→O, wherein at least one of A, B, and D is a substituted carbon atom and at most only one of A, B and D is N→O;

E and G are each hydrogen or E and G taken together form a bond (site of unsaturation);

R¹ is selected from hydrogen, alkyl, carbocycloalkyl, aryl, heterocyclo, heteroaryl, alkoxy, aryloxy, and substituted amino;

Y is selected from a bond (i.e., R¹ and X are directly linked), alkyl, carbocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclo;

X is one of C=O, C=S or SO₂;

R² is selected from carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, (heteroaryl)alkyl, aminoalkyl; substituted aminoalkyl, carboxyalkyl, alkoxyalkanoyl, aminoalkanoyl, substituted aminoalkanoyl, alkanoylamidoalkyl,

alkanoyl(substituted amido)alkyl, aroylamidoalkyl, aroyl(substituted amido)alkyl, heterocyclocarbonylamidoalkyl, heterocyclocarbonyl(substituted amido)alkyl, heteroaroylamidoalkyl, and heteroaroyl(substituted amido)alkyl;

R³ is selected from hydrogen (H), alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, (heteroaryl)alkyl, aminoalkyl; substituted aminoalkyl, carboxyalkyl, alkoxyalkanoyl, aminoalkanoyl, substituted aminoalkanoyl, alkanoylamidoalkyl, alkanoyl(substituted amido)alkyl, aroylamidoalkyl, aroyl(substituted amido)alkyl, heterocyclocarbonylamidoalkyl, heterocyclocarbonyl(substituted amido)alkyl, heteroaroylamidoalkyl, and heteroaroyl(substituted amido)alkyl;

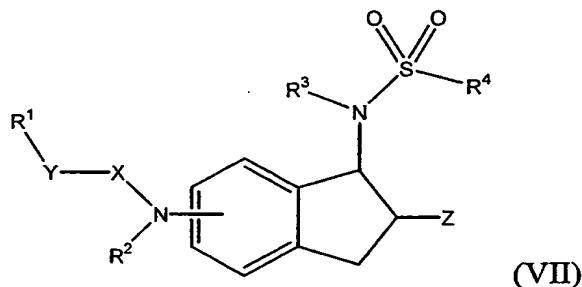
R⁴ is selected from alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heteroaryl and heterocyclo;

R⁵ and R⁶ are each independently selected from hydrogen and alkyl;

R⁷ is independently selected from hydrogen, alkyl, hydroxy, alkoxy, amino, substituted amino, nitro, cyano, halo, carboxy, alkoxycarbonyl, aminocarbonyl, substituted aminocarbonyl and n is 1, 2 or 3;

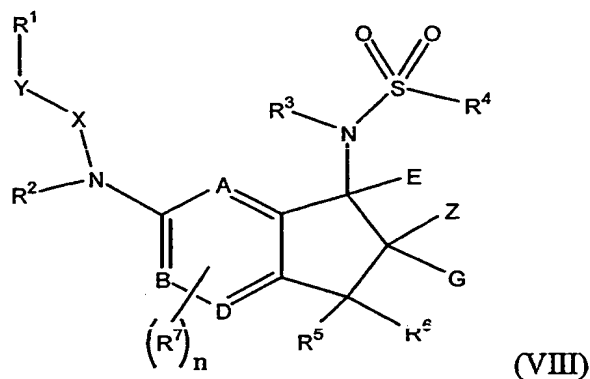
Z is selected from hydrogen, alkyl, hydroxy, SH, alkoxy, aryloxy, alkylthio, amino, substituted amino, alkoxycarbonyl, alkanoylamido, aroylamido, heterocyclocarbonylamido, heteroaroylamido, alkanoyl(alkylsubstituted) amido, aroyl(alkylsubstituted)amido, heteroaroyl(alkylsubstituted)amido, and heterocyclocarbonyl(alkyl substituted)amido;

In a preferred class of compounds of formula (VI), A, B and D are substituted carbon atoms, E, G, R⁵, R⁶ and R⁷ are each a hydrogen, Z is selected from hydrogen, alkyl, hydroxyl, amino and substituted amino and the remaining substituents are as defined above in connection with formula (VI), as is represented in the following formula (VII), (and again including the pharmaceutically acceptable salts or prodrugs thereof)



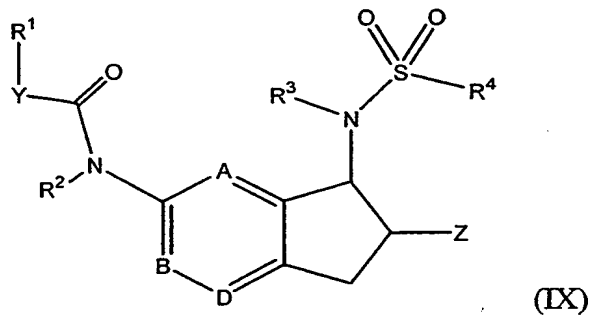
In a more preferred subset of compounds of formula (VII) (and their pharmaceutically acceptable salts, or prodrugs), R¹ is selected from H alkyl, carbocycloalkyl, aryl, and heteroaryl; X is C=O; Y is selected from a bond (i.e., R¹ and X are directly linked), alkyl, carbocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclo; R² is selected from carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl and (heteroaryl)alkyl; and R³ is selected from H, alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl and (heteroaryl)alkyl; R⁴ is selected from aryl and heteroaryl; Z is selected from H, OH, amino and substituted amino.

In still another aspect, the present invention concerns indane compounds having potassium channel inhibition activity of the formula (VIII)), or pharmaceutically acceptable salts or prodrugs thereof:



wherein all of the variables have the meaning ascribed to them in connection with formula (VI).

Yet another preferred subclass of compounds (including their pharmaceutically acceptable salts or prodrugs) falling within the compounds of formula (VI) is represent by the following formula (IX):



wherein

A, B, and D are all CH, or one of A, B, and D is a nitrogen atom or N→O;

R¹ is selected from hydrogen, alkyl, carbocycloalkyl, aryl, heterocyclo, heteroaryl, alkoxy, aryloxy and substituted amino;

Y is selected from a bond, alkyl, carbocycloalkyl, alkenyl, alkynyl, aryl,

heteroaryl and heterocyclo;

R^2 is selected from carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, (heteroaryl)alkyl, aminoalkyl; substituted aminoalkyl, carboxyalkyl, alkoxyalkanoyl and aminoalkanoyl;

R^3 is selected from hydrogen, alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, (heteroaryl)alkyl, aminoalkyl; substituted aminoalkyl, carboxyalkyl, alkoxyalkanoyl and aminoalkanoyl;

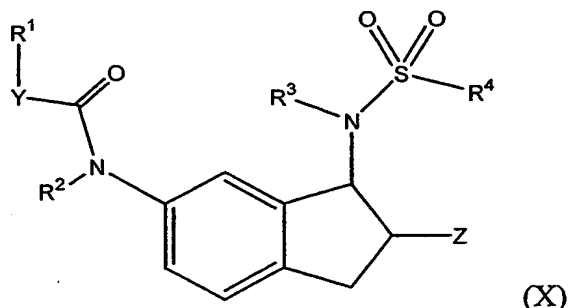
R^4 is selected from aryl, heteroaryl and heterocyclo; and

Z is selected from hydrogen, alkyl, hydroxy, SH, alkoxy, aryloxy, alkylthio, amino, substituted amino, alkoxyalkanoyl, alkanoylamido, aroylamido, heteroaroylamido, heterocyclocarbonylamido, alkanoyl(alkylsubstituted)amido, aroyl(alkylsubstituted)amido, heteroaroyl(alkylsubstituted)amido and heterocyclocarbonyl(alkylsubstituted)amido.

Preferably, R^4 in the prior embodiments is phenyl *per se* or a phenyl substituted with one or more groups in the 2 (ortho), 3 (meta), or 4 (para) positions, wherein said groups are selected from C_{1-5} alkyl, C_{1-5} alkoxy, cyano, halo and trifluoromethyl. Alternatively, R^4 is an optionally substituted heteroaryl, an optionally substituted heterocyclo or an optionally substituted carbocycloalkyl, wherein said optionally substituted moieties may be substituted with C_{1-5} alkyl, C_{1-5} alkoxy, cyano, halo and trifluoromethyl.

In a preferred class of the compounds of formula (IX) (including

pharmaceutically acceptable salts or prodrugs thereof), A, B and D are all -CH-; Z is selected from hydrogen and hydroxyl, Y is selected from a single bond, alkyl, aryl, heteroaryl and heterocyclo, R² is selected from aryl, aralkyl, heteroaryl and heteroaralkyl, and R³ is selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl, and the remaining substituents are as defined above, as is represented in the following formula (X):



Compounds, (including pharmaceutically acceptable salts or prodrugs thereof), of the prior formulae VI through X, subject to the provisos attributed to formulae I through V also are contemplated as additional aspects of the present invention.

Specific examples of molecules embraced under formulae (I) through (X) are illustrated below.

As used herein, when a particular radical generally understood to have a single point of attachment to a core structure, such as an alkyl group, is identified in connection with a structure that must have two points of attachment in the structural core (such as with the element Y in formula (I)), it is understood that the named radical, e.g., alkyl, refers to the parent radical with a hydrogen or a site of unsaturation removed to create the second point of attachment so as to provide the required structure.

The term "alkyl," as used alone or in combination herein, refers to an unsubstituted or optionally substituted, straight, or branched chain saturated

hydrocarbon group containing from one to eight carbon atoms, preferably from one to five carbons, such as methyl, ethyl, n-propyl, n-butyl, pentyl, hexyl, heptyl, octyl, the various branch chain isomers thereof, such as isopropyl, isobutyl, sec-butyl, tert-butyl, isohexyl and the like. The alkyl group may be optionally substituted by one or more substituents, and generally no more than three, and most often just one substituent. Preferred optional substituents include halo, alkoxy, amino, mono- and di-substituted amino, aryl, carboxylic acid, heterocyclo, heteroaryl, carbocycloalkyl, hydroxy, trifluoromethoxy and the like. The term "lower alkyl" refers to such alkyl groups containing from one to five carbon atoms.

The term "alkoxy," as used alone or in combination herein, refers to an alkyl group, as defined above, covalently bonded to the parent molecule through an -O- linkage, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy and the like.

The term "alkoxyalkyl" refers specifically to an alkyl group substituted with an alkoxy group.

The term "aryloxy," as used alone or in combination herein, refers to an aryl group, as defined below, covalently bonded to the parent molecule through an -O- linkage. An example of an aryloxy is phenoxy.

The term "cycloalkoxy," as used alone or in combination herein, refers to a carbocycloalkyl group, preferably a cycloalkyl group, as both defined below, covalently bonded to the parent molecule through an -O- linkage.

The term "alkylthio," as used alone or in combination herein, refers to an alkyl group, as defined above, covalently bonded to the parent molecule through an -S- linkage.

The term "alkenyl," as used alone or in combination herein, refers to an alkyl group, as defined above, containing one or more carbon-to-carbon double bonds, preferably one or two double bonds. Examples of alkenyl include

ethenylene, propenylene, 1, 3- butadienyl, and 1, 3, 5-hexatrienyl.

The term "alkynyl," as used alone or in combination herein, refers to an alkyl group, as defined above, containing one or more carbon-to-carbon triple bonds, preferably one or two triple bonds.

The term "cycloalkyl," as used alone or in combination herein, refers to an unsubstituted or optionally substituted, saturated cyclic hydrocarbon group containing three to eight carbon atoms. The cycloalkyl group may optionally be substituted by one or more substituents, and generally no more than three, and most often just one substituent. Preferred optional substituents include alkyl, halo, amino, mono- and di-substituted amino, aryl, hydroxy and the like.

The term "haloalkyl" is a species of alkyl as defined herein, and particularly refers to an alkyl, preferably a lower alkyl, substituted with one or more halogen atoms, and preferably is a C₁ to C₄ alkyl substituted with one to three halogen atoms. One example of a haloalkyl is trifluoromethyl.

The term "alkanoyl" as used alone or in combination herein refers to an acyl radical derived from an alkanecarboxylic acid (alkyl-C(O)-), particularly a lower alkanecarboxylic acid, and includes such examples as acetyl, propionyl, butyryl, valeryl, and 4-methylvaleryl.

The term "aroyl" means an acyl radical derived from an aromatic carboxylic acid, such as optionally substituted benzoic or naphthoic acids and specifically including benzoyl and 1-naphthoyl.

The term "aminocarbonyl" means an amino-substituted carbonyl (carbamoyl or carboxamide) wherein the amino group is a primary amino ($-NH_2$). Substituted aminocarbonyl refers to secondary (mono-substituted amino) or tertiary amino (di-substituted amino) group, as defined below, preferably having as a substituent(s) a lower alkyl.

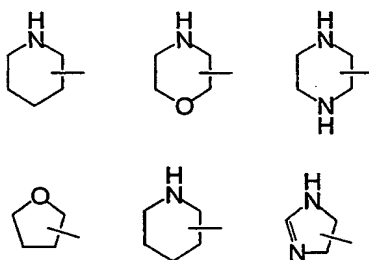
The term "aminoalkanoyl" means an amino-substituted alkanoyl wherein

the amino group is a primary amino ($--alkyl-C(O)-NH_2$). The term "substituted aminoalkanoyl" refers to related secondary (mono-substituted amino) or tertiary amino (di-substituted amino) group, as defined below.

The term "carbocycloalkyl" when used alone or in combination refers to an unsubstituted or optionally substituted, stable, saturated or partially unsaturated monocyclic, bridged monocyclic, bicyclic, and spiro ring carbocycles of 3 to 15 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclohexyl, bicyclooctyl, bicyclononyl, spirononyl and spirodecyl. Cycloalkyls are thus one specific subset of carbocycloalkyls, and in the context of the present invention constitute a highly preferred subset. The term "optionally substituted" as it refers to "carbocycloalkyl" herein indicates that the carbocycloalkyl group may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups. Generally, there is no more than one optional substituent.

The term "heterocyclo" as used, alone or in combination, herein refers to an unsubstituted or optionally substituted, stable, saturated, or partially unsaturated, monocyclic, bridged monocyclic, bicyclic, and spiro ring system containing carbon atoms and other atoms selected from nitrogen, sulfur and/or oxygen. Preferably, a heterocyclo is a 5 or 6-membered monocyclic ring or an 8-11 membered bicyclic ring which consists of carbon atoms and contains one, two, or three heteroatoms

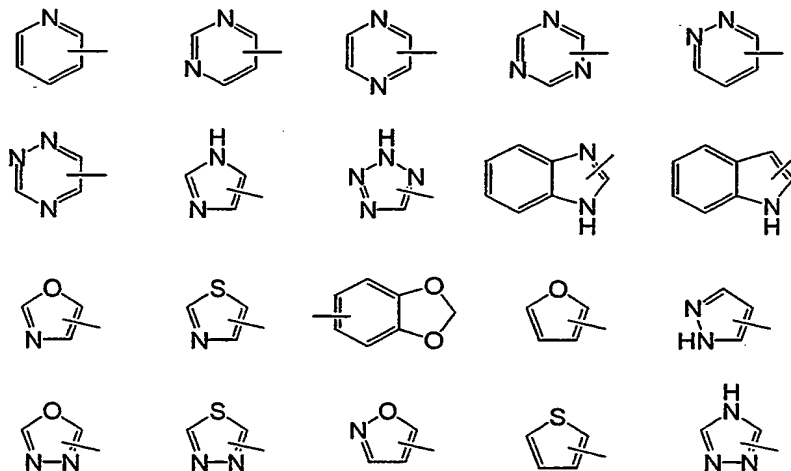
selected from nitrogen, oxygen and/or sulfur. Heterocyclo includes benz-fused monocyclic carbocycloalkyl groups having at least one such heteroatom. The term "optionally substituted" as it refers to "heterocyclo" herein indicates that the heterocyclo group may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl and including haloalkyl (preferably trifluoromethyl)), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups. Generally, there is no more than one optional substituent. Several non-limiting examples of such heterocyclo groups are illustrated below:



The heterocyclo group may be, and generally is attached to the parent structure through a carbon atom, or alternatively may be attached through any heteroatom of the heterocyclo that results in a stable structure.

The term "heteroaryl" as used alone or in combination, herein refers to an unsubstituted or optionally substituted, stable, aromatic monocyclic or bicyclic ring system containing carbon atoms and other atoms selected from nitrogen, sulfur

and/or oxygen. Preferably, a heteroaryl is a 5 or 6-membered monocyclic ring (optionally benzofused) or an 8-11 membered bicyclic ring which consists of carbon atoms and contains one, two, or three heteroatoms selected from nitrogen, oxygen and/or sulfur. The term "optionally substituted" as it refers to "heteroaryl" herein indicates that the heteroaryl group may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl and including haloalkyl (preferably trifluoromethyl)), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino, cyano, halo, alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups. Generally, there is no more than one optional substituent. Several non-limiting examples of such heteroaryl groups are illustrated below:



The heteroaryl group may be, and generally is attached to the parent structure

through a carbon atom or alternatively may be attached through any heteroatom of the heteroaryl that results in a stable structure. In the foregoing structures it also is contemplated that a nitrogen could be replaced with an N-oxide.

Both heterocyclo and heteroaryl also are intended to embrace benzo fused structures such as 1, 2-methylenedioxybenzene and 1, 4-benzodioxan.

The specific chemical nature of the optionally substituted heterocyclo and heteroaryl groups for the terminal moieties R^1 and R^2 in the prior identified potassium channel inhibitor compounds is not narrowly critical and, as noted above, a wide variety of substituent groups are contemplated. Preferably, the substituents for the heterocyclo and heteroaryl groups are selected such that the total number of carbon and hetero atoms comprising the substituted heterocyclos and heteroaryls is no more than about 20.

The terms "halo" and "halogen" as used herein to identify substituent moieties, represent fluorine, chlorine, bromine or iodine, preferably chlorine or fluorine.

The term "aryl," when used alone or in combination, refers to an unsubstituted or optionally substituted monocyclic or bicyclic aromatic hydrocarbon ring system having 6 to 12 ring carbon atoms. Preferred are optionally substituted phenyl, 1-naphthyl, or 2-naphthyl groups. The aryl group may optionally be substituted at one or more substitutable ring positions (generally at no more than three positions and most often at one or two positions) by one or more groups independently selected from alkyl (including haloalkyl (preferably trifluoromethyl and difluoromethyl)), alkenyl, alkynyl, alkoxy, aryloxy, nitro, hydroxy, amino, mono- and di-substituted amino, cyano, halo, alkanoyl, aminocarbonyl, carboxylic acid, carboxylic acid esters, carboxylic acid amide, an optionally substituted phenyl (optionally substituted by halo, lower alkyl and lower alkoxy groups), heterocyclo, or heteroaryl. Preferably, the aryl group is phenyl optionally substituted with up to

four and more usually with one or two groups, preferably selected from lower alkyl, lower alkoxy, as well as cyano, trifluoromethyl and halo.

The terms "aralkyl" and "(aryl)alkyl," alone or in combination are a species of alkyl as defined herein, and particularly refers to an alkyl group as defined above in which one hydrogen atom is replaced by an aryl group as defined above, and includes benzyl, and 2-phenylethyl.

The terms "(heterocyclo)alkyl" and "(heteroaryl)alkyl" alone or in combination can be considered a species of alkyl as defined herein, and particularly refers to an to an alkyl group as defined above in which one hydrogen atom is replaced by a heterocyclo group as defined above, or by a heteroaryl group as defined above.

The term "alkoxycarbonyl" alone or in combination means a radical of the formula -C(O)-alkoxy , in which alkoxy is as defined above.

The term "alkylcarbonyloxy" alone or in combination means a radical of the formula -O-C(O)-alkyl , in which alkyl is as defined above.

The term "alkoxyalkanoyl" alone or in combination means a radical of the formula $\text{--alkyl-C(O)-O-alkyl}$.

The term "carboxyalkyl" alone or in combination means a radical of the formula --alkyl-C(O)-OH .

As used in connection with formula (I) and elsewhere in this application, the term "substituted carbon atom" means, a ring carbon substituted with one of the group R^7 , or the radical $\text{-N(R}^2\text{)(XYR}^1\text{)}$.

The term "substituted amino" embraces both "mono and di-substituted amino." These terms, alone, or in combination, mean a radical of the formula -NR'R'' , where, in the case of mono-substitution, one of R' and R'' is a hydrogen and the other is selected from alkyl, carbocycloalkyl, aryl, heterocyclo, (aryl)alkyl, (heterocyclo)alkyl, heteroaryl and hetero(aryl)alkyl; in the case of di-substitution, R'

and R" are independently selected from alkyl, carbocycloalkyl, aryl, heterocyclo, and heteroaryl, or R' and R" together with the nitrogen atom to which they are both attached form a three to eight-membered heterocyclo or heteroaryl radical.

The term "amido" refers to the group (-NH-) and the term "substituted amido" embraces a radical of the formula (-NR'-) where R' has the meaning above in connection with substituted amino.

The terms "alkanoylamido," "aroylamido," "heterocyclocarbonylamido" and "heteroaroylamido" mean groups of the formula R-C(O)-NH-- where R is an alkyl, aryl, heteroaryl or heterocyclo.

The terms "heteroaroyl" and "heterocyclocarbonyl" when used alone or in combination means groups of the formula R-C(O)-- where R is a heteroaryl or heterocyclo.

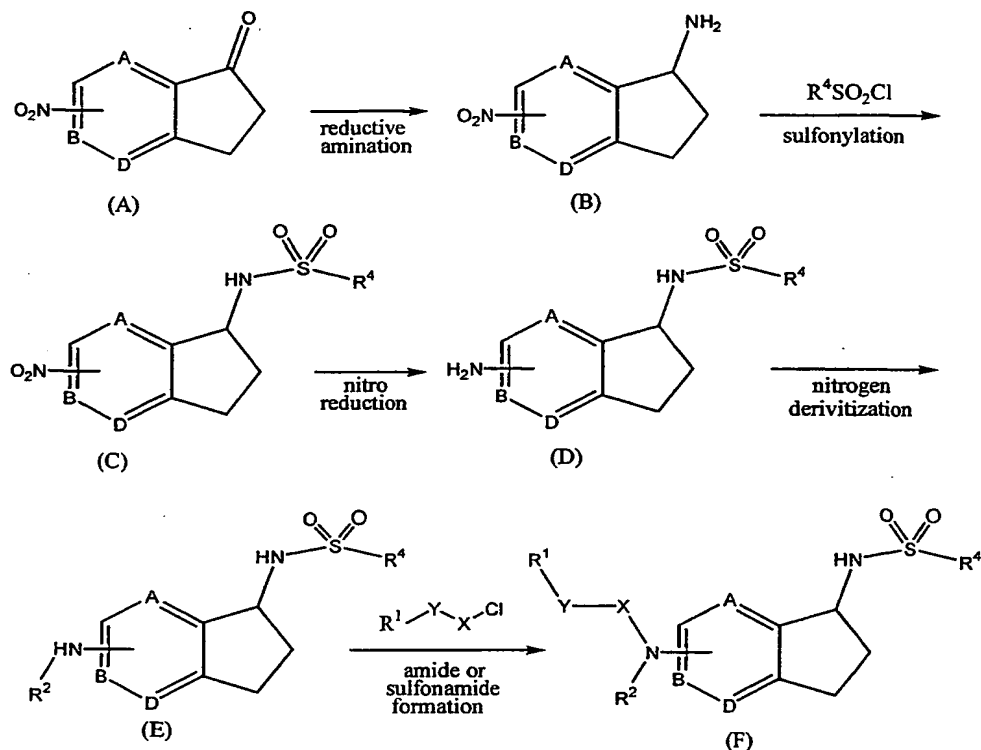
Unless otherwise defined, the term "optionally substituted" as used herein, refers to the substitution of a ring system at one or more positions with one or more groups selected from: C₁₋₅ alkyl, C₁₋₅ alkoxy, an optionally substituted phenyl, cyano, halo, trifluoromethyl, C₁₋₅ alkoxy carbonyl, C₁₋₅ alkyl carbonyloxy, mono- and bis-(C₁₋₅ alkyl)-carboxamide, C₁₋₅ alkyl amido, nitro, and mono- and bis-(C₁₋₅ alkyl)-amino.

Applicants recognize that there may be some overlap in some of the definitions of the various radical groups. Specific groups are mentioned, however, such as (aryl)alkyl, and may be particularly identified in the claims, in order to emphasize their positive inclusion in the described subject matter, as not only an optional substituent.

The term "treating" as used herein, describes the management and care of a patient afflicted with a condition, disease or disorder for which the administration of a compound of the present invention alters the action or activity of a potassium channel to prevent the onset of symptoms or complications associated with the

condition, disease or disorder, to alleviate the symptoms or complications caused by the condition, disease or disorder, or to eliminate the condition, disease or disorder altogether.

Certain indane compounds of the previous formulae useful as potassium channel inhibitors in accordance with the present invention can be prepared in accordance with the following Scheme 1:



SCHEME 1

Compounds of the invention of formula II where Z is hydrogen may be prepared starting with a nitro indanone (A), which in step (1) is reductively aminated in the presence of ammonium acetate (employing a molar ratio of nitro indanone:ammonium acetate within the range from about 1:1 to about 1:30) and a reducing agent such as sodium cyanoborohydride in an inert organic solvent such as

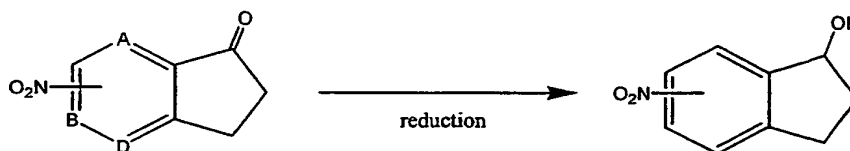
methanol to form the nitro-amino compound (B). The nitro-amino compound (B) then is reacted with a sulfonylating agent (employing a molar ratio of Step (1) product to sulfonylating agent within the range from about 1:1 to about 10:1) in the presence of a base such as triethylamine or pyridine and in an inert organic solvent such as tetrahydrofuran or dichloromethane to form the sulfonylated compound (C).

The sulfonylated compound (C) is then subjected to nitro-reduction by treatment with a suitable reducing agent such as sodium borohydride in the presence of nickel chloride in an organic solvent such as tetrahydrofuran and/or methanol to form the aniline (D). Aniline (D) is then derivatized by treatment with an alkylating agent such as an alkyl halide (R^2X where X is Cl, Br, or I) in the presence of a base such as potassium carbonate in an inert solvent such as acetonitrile to form the secondary amine (E). Alternatively, aniline (D) can be derivatized by reductive alkylation using an aldehyde and a drying agent such as sodium sulfate followed by treatment with a reducing agent such as sodium borohydride in an organic solvent such as methanol or ethanol.

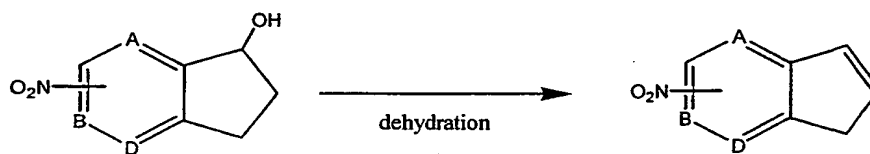
The secondary amine (E) thereafter undergoes an acylation in step (5) by reacting the secondary amine (E) with an acylating agent such as an acid chloride (which may be prepared *in situ* from the corresponding carboxylic acid by methods known in the literature) in the presence of a base such as triethylamine or pyridine in an inert organic solvent such as tetrahydrofuran or dichloromethane to form the amide compounds (F) of formula II where X is C=O. The secondary amine (E) can also be reacted with a sulfonylating agent under conditions described above to form sulfonamide compounds of formula II (compound (F)) where X is SO₂. The secondary amine (E) can also be reacted with an isocyanate in an organic solvent such as tetrahydrofuran or dichloromethane to form urea compounds of formula II where X is C=O, Y is a bond, and R¹ is a substituted amino.

The starting nitro indanone, compound (A), the amino compound (B), the sulfonamide (C), and the aniline (D) in General Scheme 1 may be prepared as described in N. Castle et al., WO 9804521, see also U.S. 6,083,986 incorporated herein by reference..

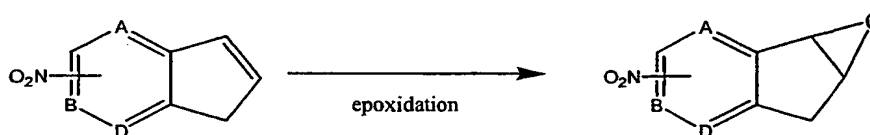
A synthetic approach to prepare compounds of formula II where Z is hydroxyl is provided by the following Scheme 2 (Steps 1-8). In step (1), reduction of a nitro indanone (using NaBH₄ for example) gives the corresponding alcohol;



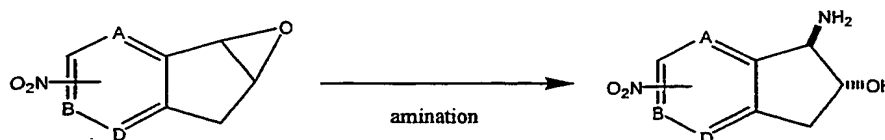
In the next step (2), the product of step (1) is subjected to an acid catalyzed dehydration (pTSA/Toluene) to give the corresponding indene.



Then in step (3) the double bond of the indene product of step (2) is oxidized (*e.g.* using M-CPBA/CH₂Cl₂) to give the corresponding epoxide.

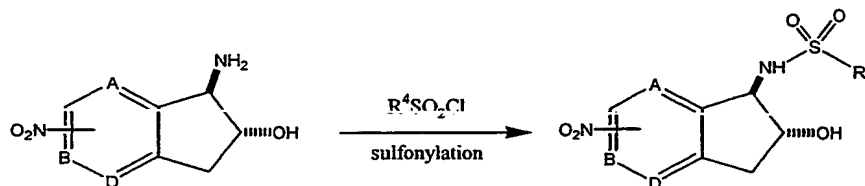


In step (4), the epoxide of step (3) is aminated (for instance using ammonium hydroxide) to give the corresponding amino alcohol.

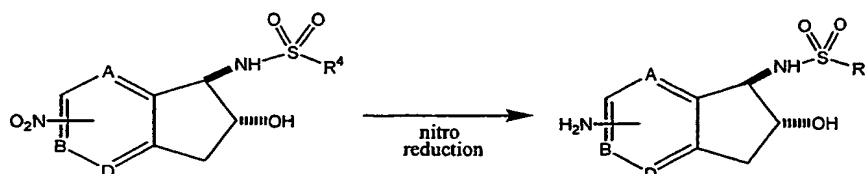


The amino-alcohol of step (4) is sulfonylated, for example using a sulfonyl chloride,

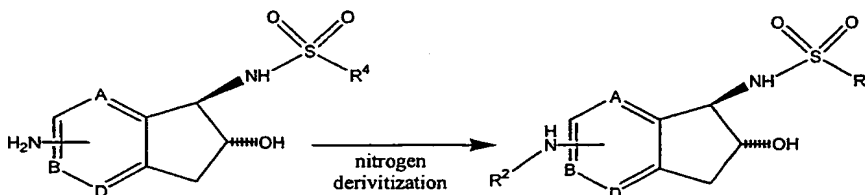
to attach an R^4 -SO₂- moiety. The amino-alcohol is reacted in a suitable solvent with the sulfonyl chloride (or a sulfonyl anhydride) in the presence of an acid scavenger. Suitable solvents in which the reaction can be conducted include methylene chloride and tetrahydrofuran. Suitable acid scavengers include triethylamine and pyridine.



In step (6), the nitro moiety of the sulfonlated product of step (5) is reduced (SnCl₂) to give the corresponding aniline.

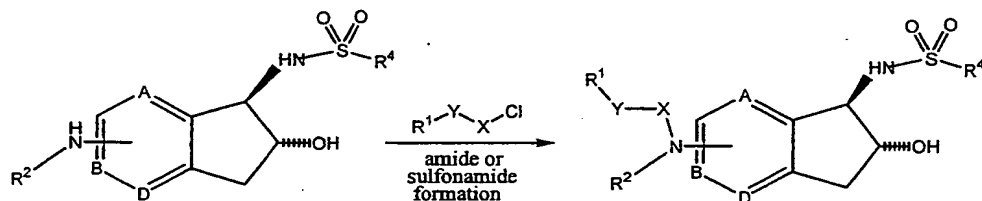


The aniline formed in step (6) can then be derivatized (step (7)) by treatment with an alkylating agent such as an alkyl halide (R^2X where X is Cl, Br, or I) in the presence of a base such as potassium carbonate in an inert solvent such as acetonitrile to form a secondary amine. Alternatively, the aniline formed in step (6) can be derivatized by reductive alkylation using an aldehyde and a drying agent such as sodium sulfate followed by treatment with a reducing agent such as sodium borohydride in an organic solvent such as methanol or ethanol.



As in Scheme 1, the so-formed secondary amine thereafter undergoes an acylation in step (8) with an acylating agent such as an acid chloride (which may be prepared *in*

situ from the corresponding carboxylic acid by methods known in the literature) in the presence of a base such as triethylamine or pyridine in an inert organic solvent such as tetrahydrofuran or dichloromethane to form the desired amide where X is C=O. The resulting amide (X is C=O) can be readily converted to the corresponding thioamide (X is C=S) via known literature procedures (e.g., through the use of Lawesson's reagent. The secondary amine could also be reacted with a sulfonylating agent under conditions described above to form the related sulfonamide compounds where X is SO₂. Additionally, the secondary amine could also be reacted with an isocyanate in an organic solvent such as tetrahydrofuran or dichloromethane to form a urea where X is C=O, Y is a bond, and R¹ is a substituted amino.



Those skilled in the art will appreciate additional techniques and raw materials suitable for preparing other compounds falling within the scope of the present invention, as for example are illustrated in the subsequent specific examples. For instance, the skilled worker will readily appreciate the advantage of employing protecting groups, and will readily understand their application in a specific synthetic approach to improve the yield of desired products. For example, one skilled in the art will recognize that there are a variety of protecting groups as discussed in "Protective Groups in Organic Synthesis", T.W. Green and P.G.M. Wuts (1999).

It is recognized that there is generally at least one and often more than one chiral center in the compounds falling within the scope of the present invention and thus such compounds will exist as various stereoisomeric forms. Applicants intend

to include all the various stereoisomers within the scope of the invention. Thus, this invention is intended to include the cis and trans isomers and the corresponding enantiomers of the compounds of formula I-V. Though the compounds may be prepared as racemates and can conveniently be used as such, individual enantiomers also can be isolated or preferentially synthesized by known techniques if desired. Such racemates and individual enantiomers and mixtures thereof are intended to be included within the scope of the present invention.

The present invention also encompasses the pharmaceutically acceptable prodrugs of the compounds of Formula I. A prodrug is a drug which has been chemically modified and may be biologically inactive at its site of action, but which is degraded or modified by one or more enzymatic or other *in vivo* processes to the parent bioactive form. Generally, a prodrug has a different pharmacokinetic profile than the parent drug such that, for example, it is more easily absorbed across the mucosal epithelium, it has better salt formation or solubility and/or it has better systemic stability (e.g., an increased plasma half-life).

Those skilled in the art recognize that chemical modifications of a parent drug to yield a prodrug include: (1) terminal ester or amide derivatives which are susceptible to being cleaved by esterases or lipases; (2) terminal peptides which may be recognized by specific or nonspecific proteases; or (3) a derivative that causes the prodrug to accumulate at a site of action through membrane selection, and combinations of the above techniques. Conventional procedures for the selection and preparation of prodrug derivatives are described in H. Bundgaard, *Design of Prodrugs*, (1985). Those skilled in the art are well-versed in the preparation of prodrugs and are well-aware of its meaning.

The compounds of the present invention can be used in their neat form or in the form of pharmaceutically-acceptable salts derived from inorganic or organic acids, or in the form of their esters, amides, complexes, chelates, hydrates,

stereoisomers, crystalline or amorphous forms, metabolites, metabolic precursors, or prodrugs. In the practice of the present invention, compounds of the present invention in their neat form will generally have a molecular weight of 800 or below, usually 600 or below.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts of compounds of the present invention include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as maleic acid, succinic acid and citric acid. These salts thus include, but are not limited to, the following : acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates, like dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others. Water or oil soluble or dispersible products are thereby generally obtained.

The pharmaceutically acceptable salts of the compounds of the present invention also can exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates also can be prepared. Such solvates are within the scope of the present invention.

The pharmacological profile of the potassium channel inhibitory activity of

the compounds of the present invention can be readily assessed by those skilled in the art using routine experimentation, such as the procedures and techniques illustrated in the examples which follow. Assays for assessing the activity of particular compounds may employ cells stably transfected to express a specific potassium channel, as well as native mammalian cells. In particular, stable transfected cells, transfected to express a specific potassium channel, which have been treated with a voltage dependent fluorescent dye, such as *bis*-(1,3-dibutylbarbituric acid)trimethine oxonol, can be used to gauge the inhibitory activity of potassium channel inhibitor compounds, possibly in comparison to known inhibitors. Alternatively, such cells can be primed with a detectible species, such as ^{86}Rb , and then challenged with a particular compound, under conditions otherwise suitable for activating the potassium channel, to assess the potassium inhibitory activity of the compound. The potassium channel inhibitory activity of a compound also can be determined using isolated mammalian cells and the whole cell configuration of the known patch clamp technique (Hamill et al., *Pflügers Archiv* 391:85, 1981). These and other known techniques can be readily employed by those skilled in the art to assess the activity level of the potassium channel inhibitor compounds of the present invention.

The compounds of the present invention may be administered by a variety of routes including orally, parenterally, sublingually, intranasally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intracardiac injection, or infusion techniques. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices.

Injectable preparations, for example, sterile injectable aqueous or oleaginous

suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,2-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from

phospholipids or other lipid substances. Liposomes are formed as mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33, et seq.

To select preferred compounds from less preferred compounds, one uses by example the *in vitro* assays detailed under the sub-heading **BioAssays** hereafter described. Typically, a preferred compound will produce half maximal blocking activity at a concentration below about 5 μ M, preferably below about 1 μ M, more preferably below about 100nM and most preferably below about 10nM in the *in vitro* assays described. One of ordinary skill will recognize that the final and optimum dose and regimen will be determined empirically for any given drug.

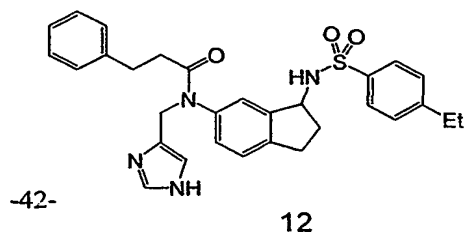
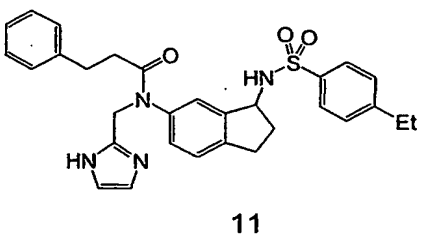
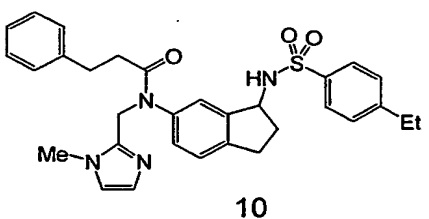
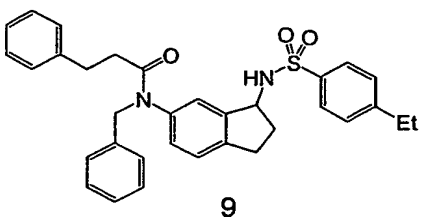
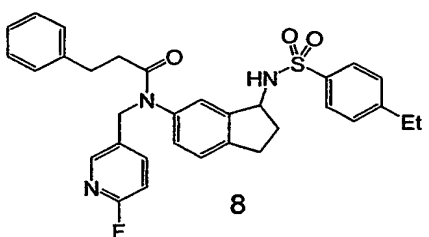
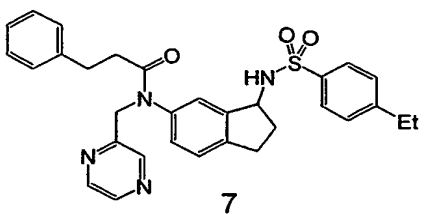
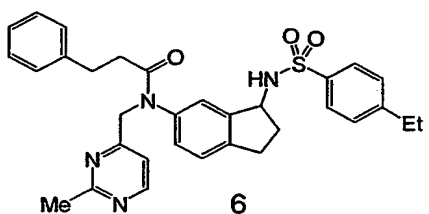
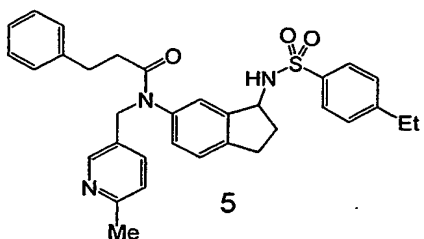
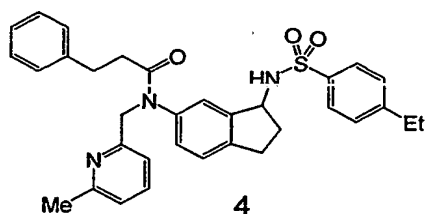
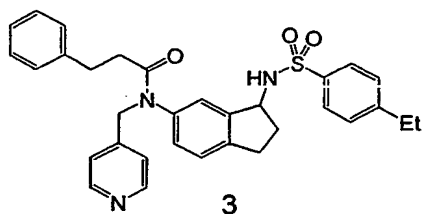
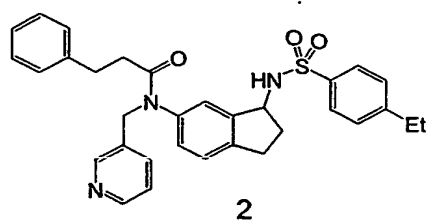
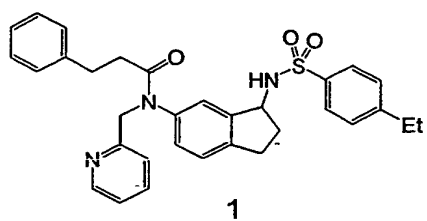
Total daily dose administered to a host in single or divided doses may be an amount, for example, from 0.001 to 100 mg of active ingredient per kg body weight on a daily basis and more usually 0.01 to 10 mg/kg/day. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose. It is anticipated that a therapeutically effective serum concentration of active ingredient will be 10 nM to 10 μ M (5ng/ml to 5 μ g/ml).

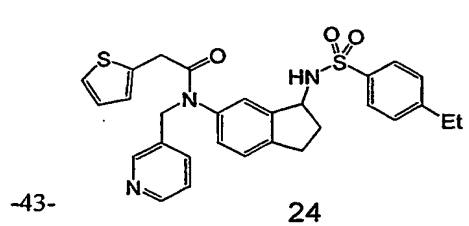
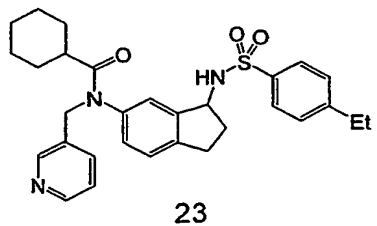
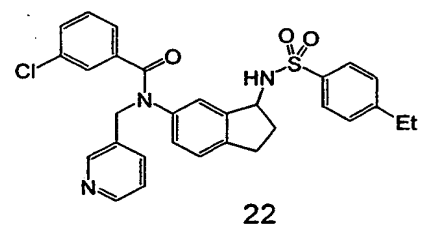
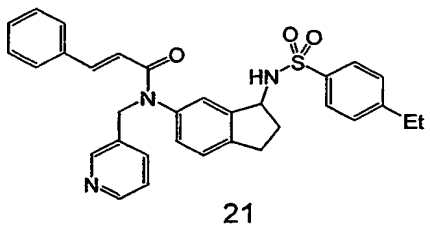
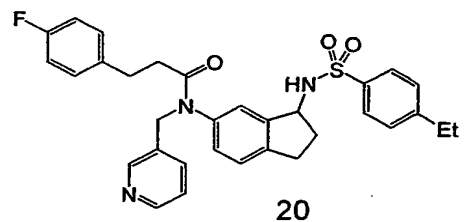
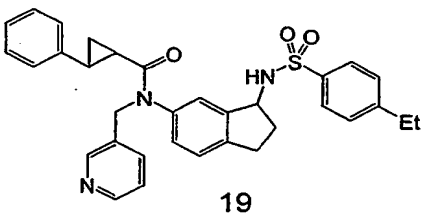
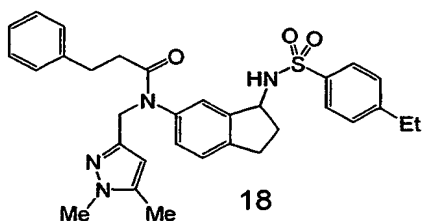
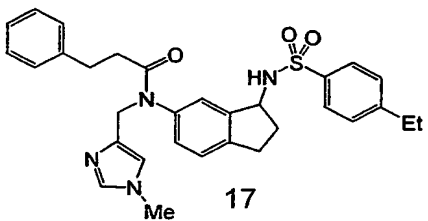
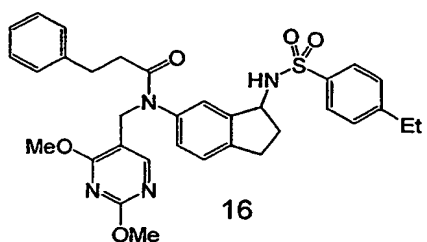
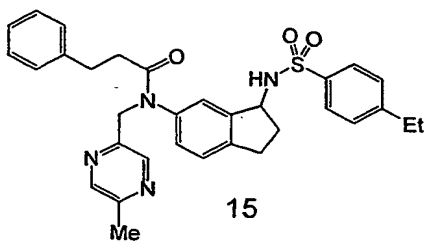
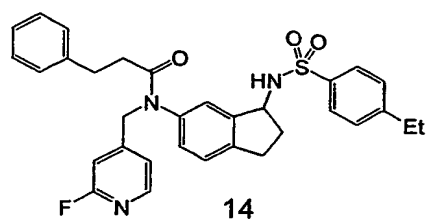
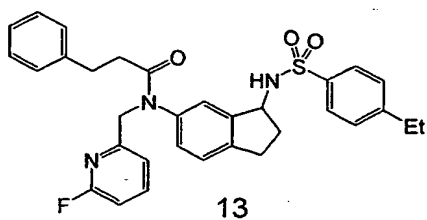
The amount of active ingredient that may be combined with carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

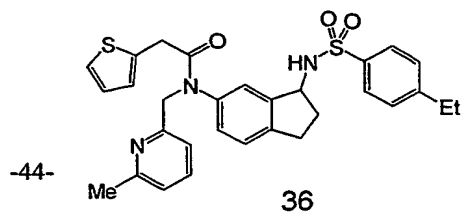
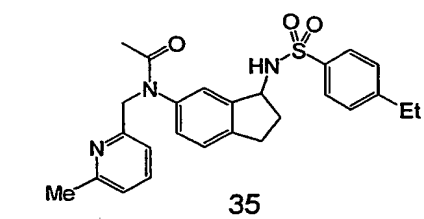
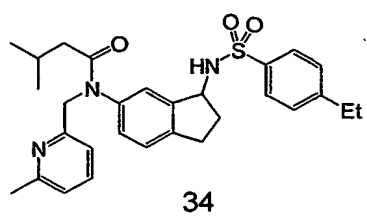
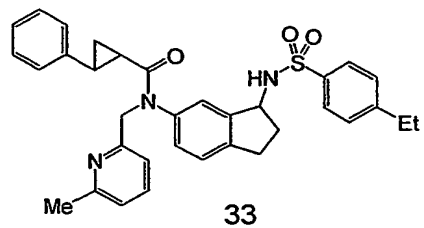
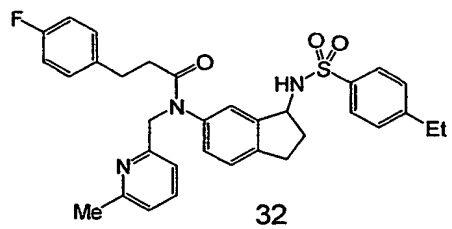
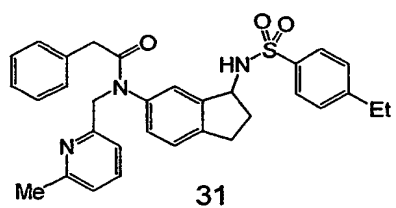
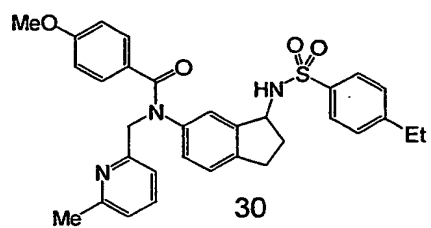
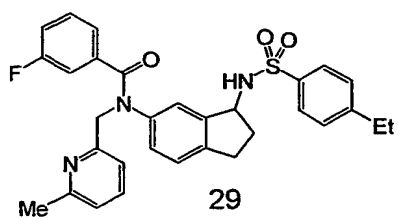
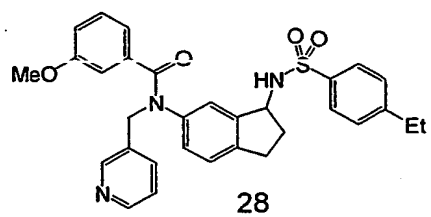
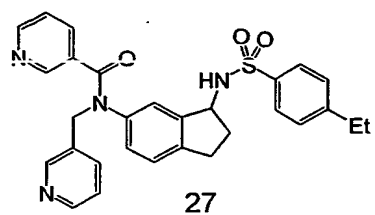
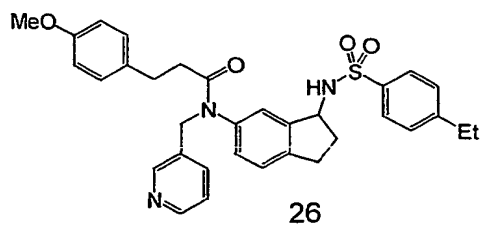
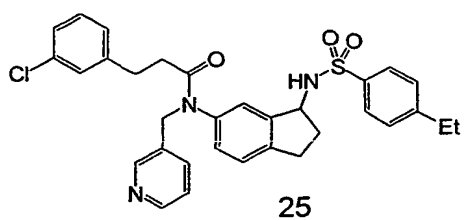
It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific

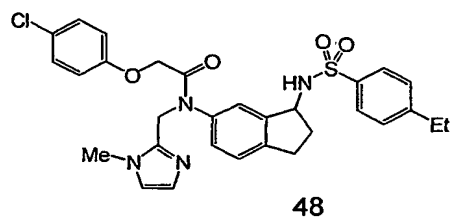
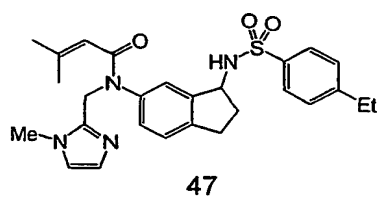
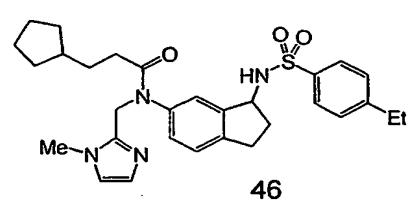
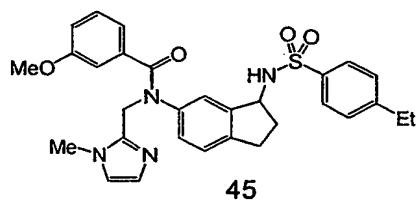
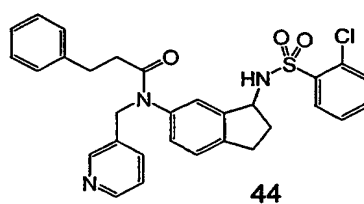
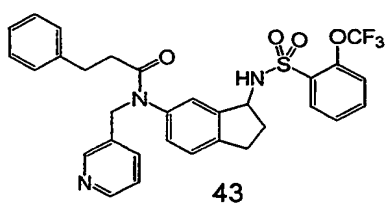
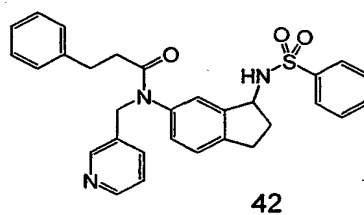
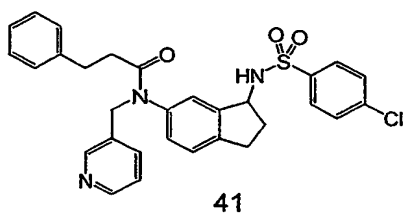
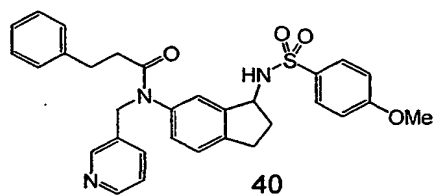
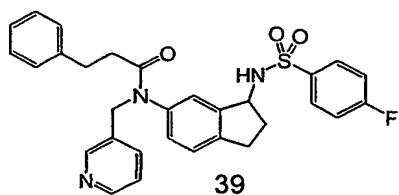
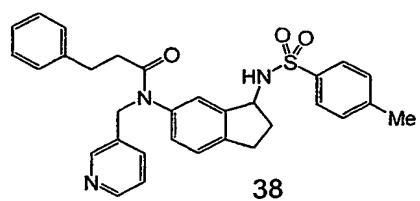
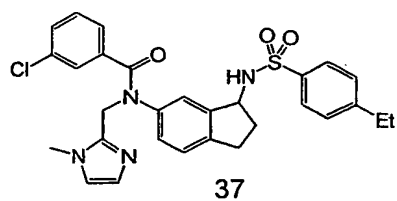
compound employed, the age, body weight, general health, sex, and diet of the patient, the time of administration, the route of administration, the rate of excretion, whether a drug combination is used, and the severity of the particular disease.

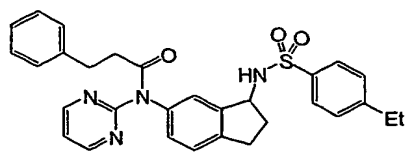
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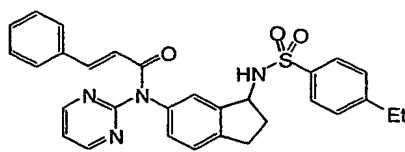




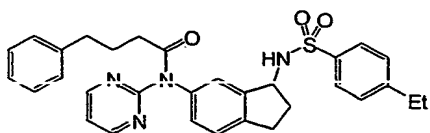




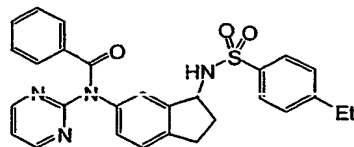
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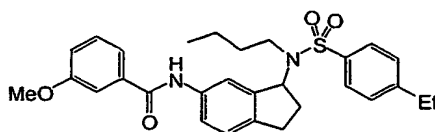
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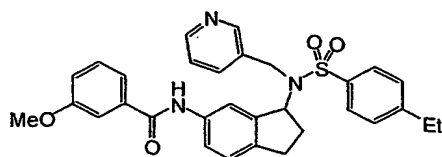
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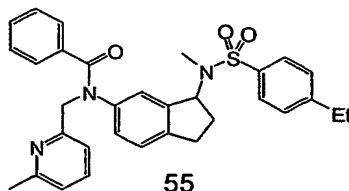
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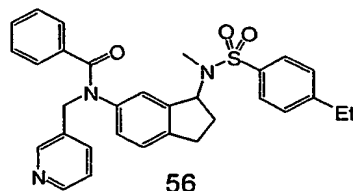
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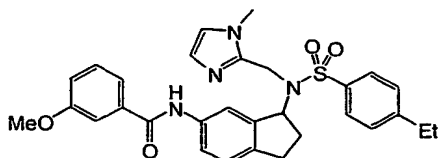
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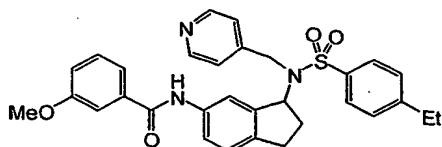
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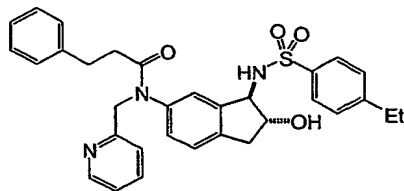
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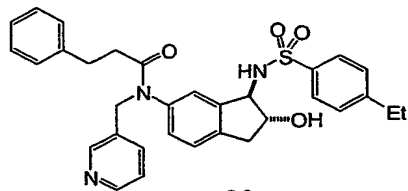
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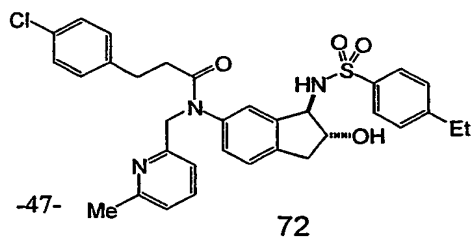
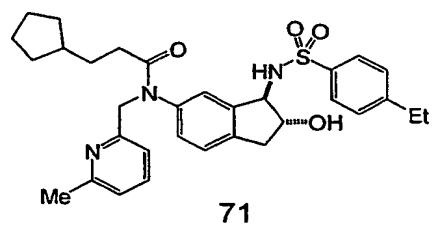
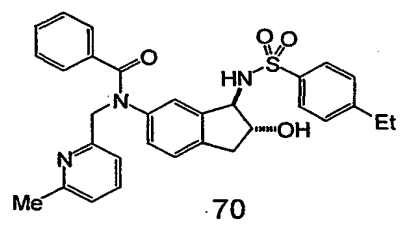
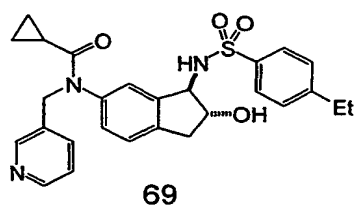
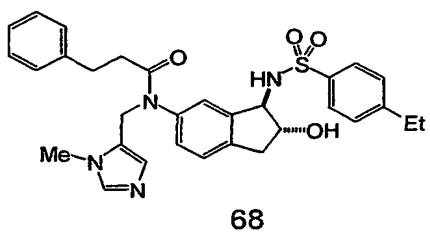
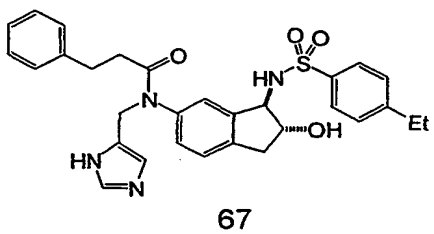
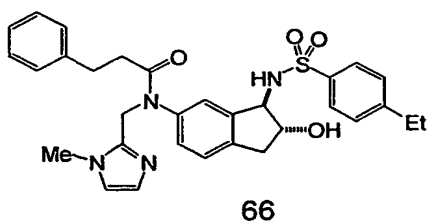
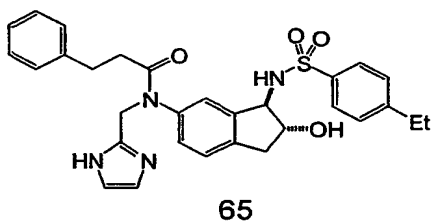
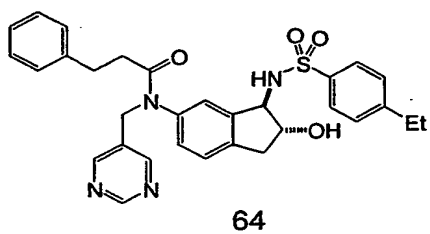
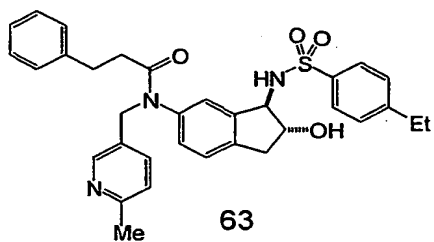
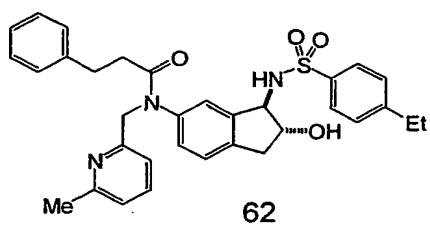
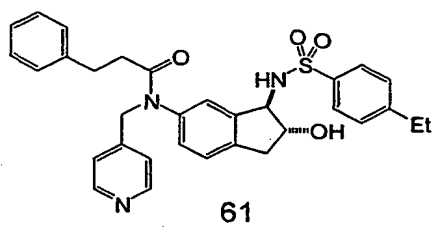
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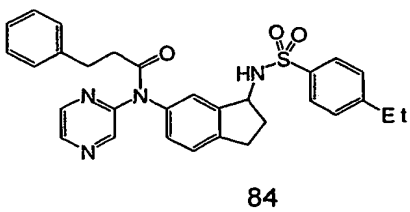
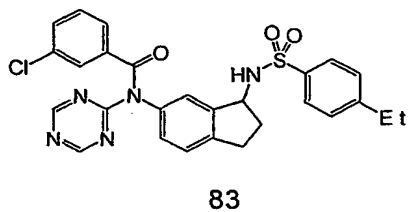
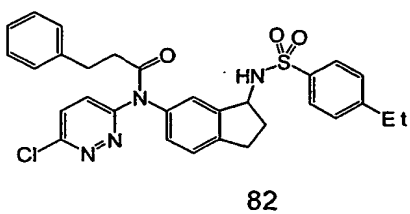
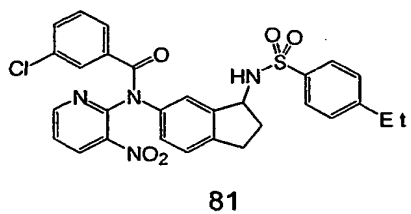
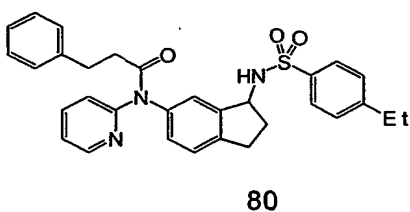
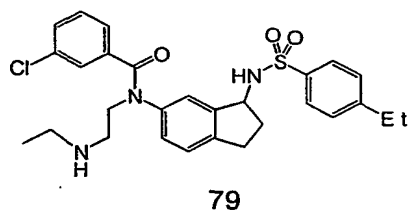
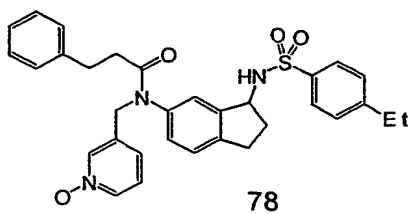
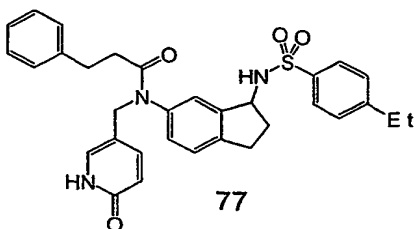
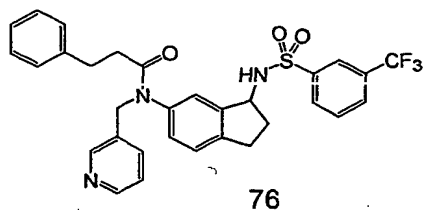
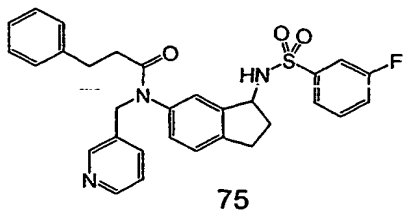
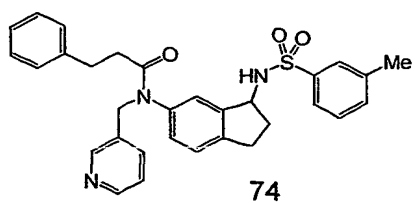
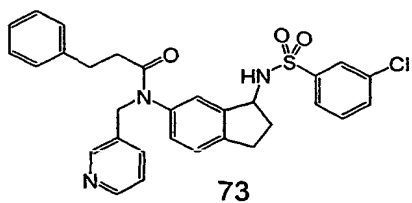


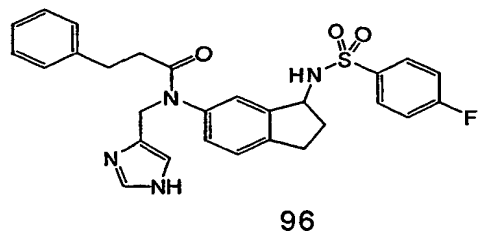
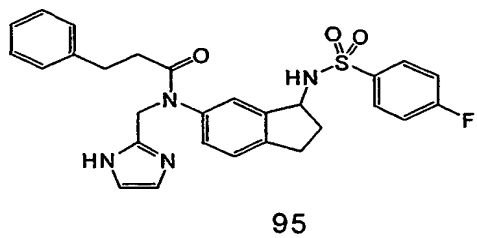
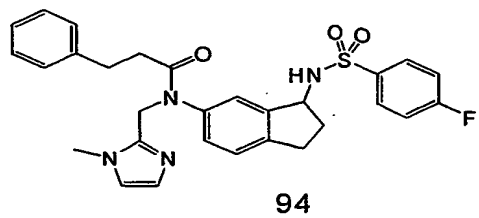
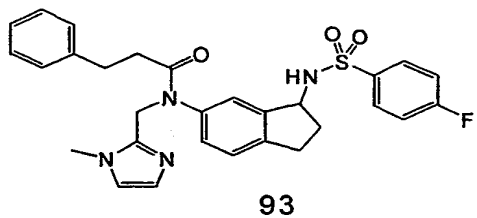
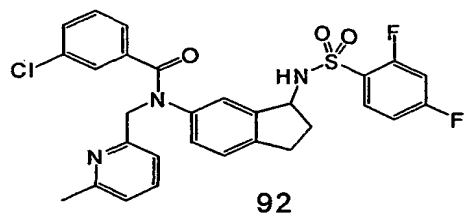
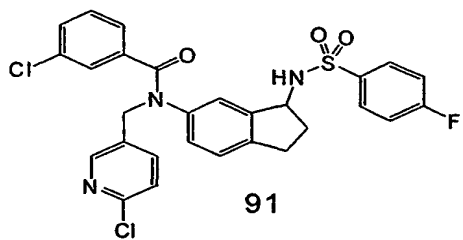
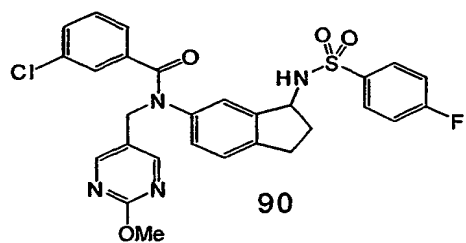
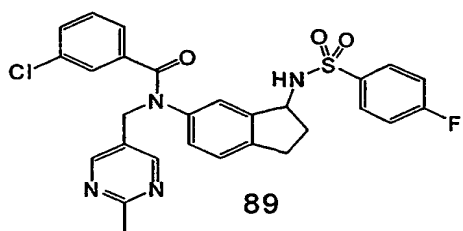
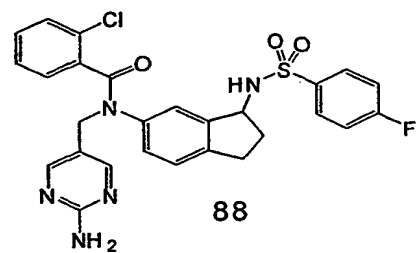
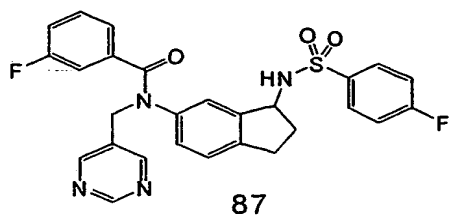
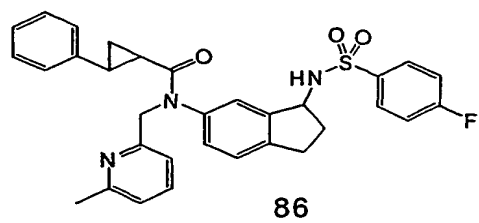
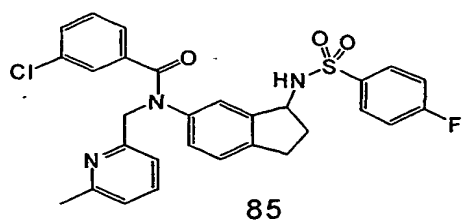
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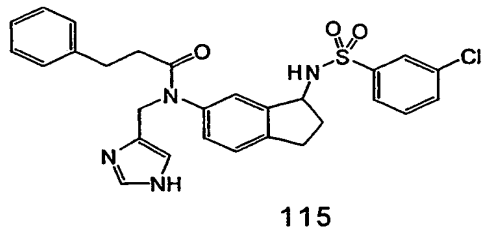
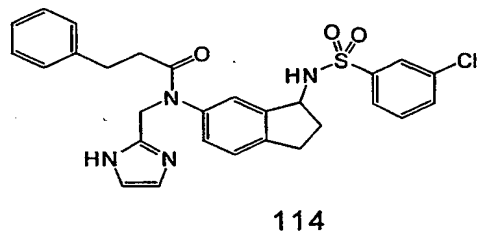
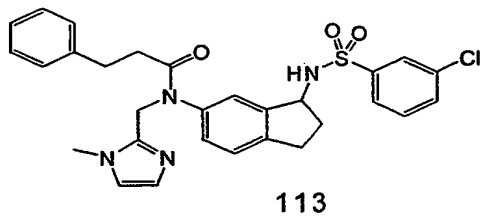
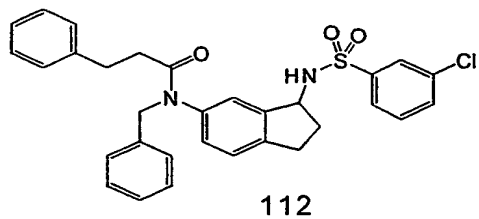
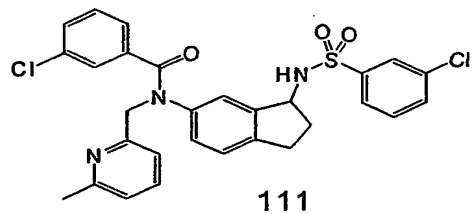
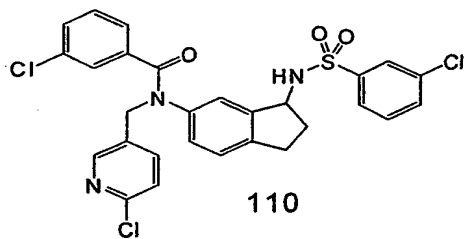
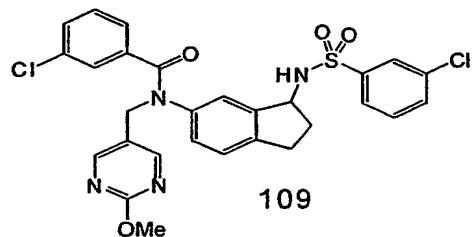
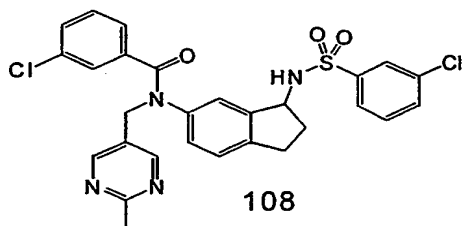
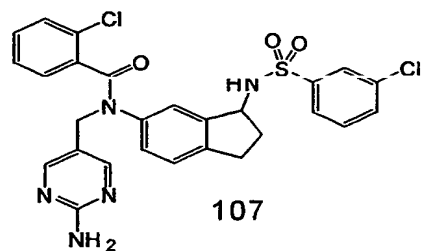
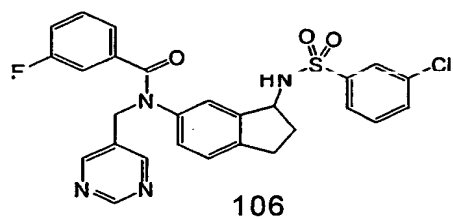
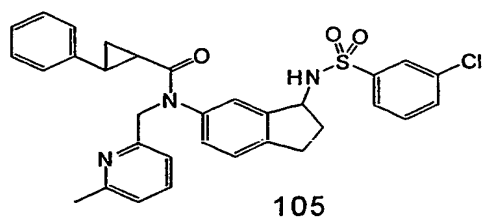
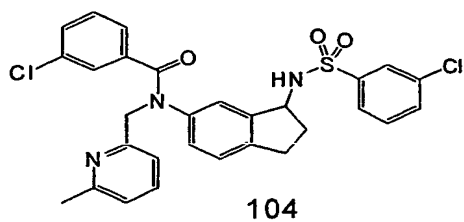


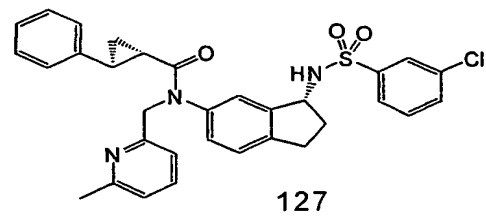
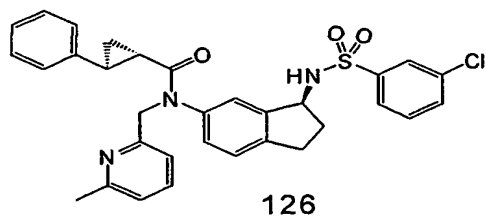
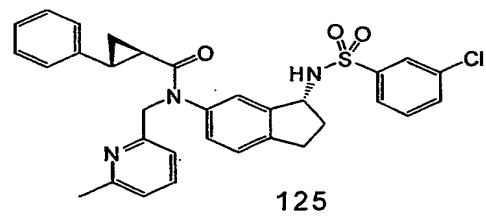
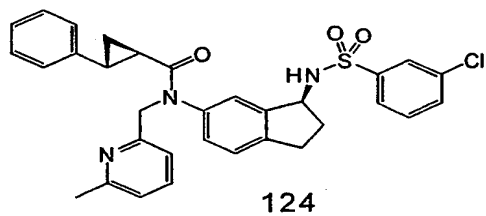
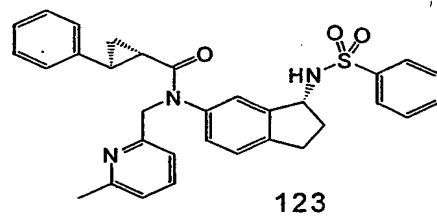
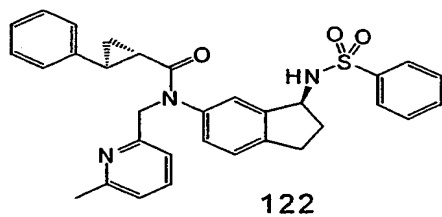
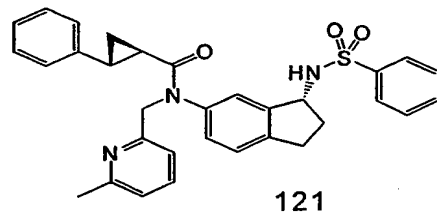
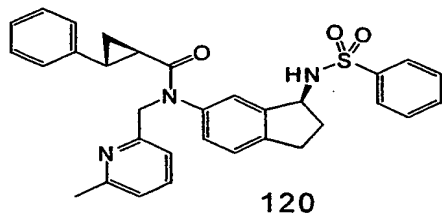
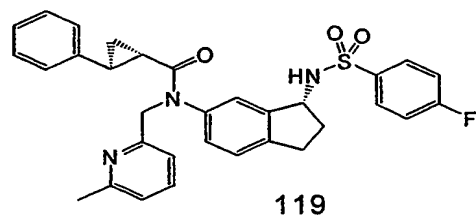
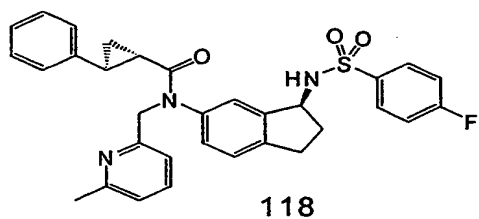
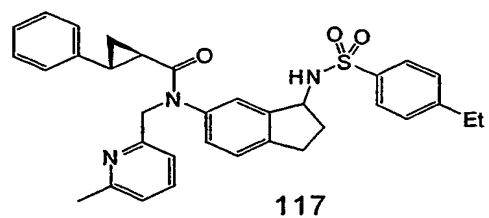
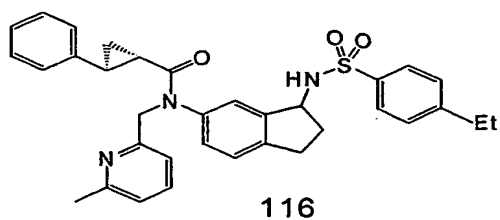
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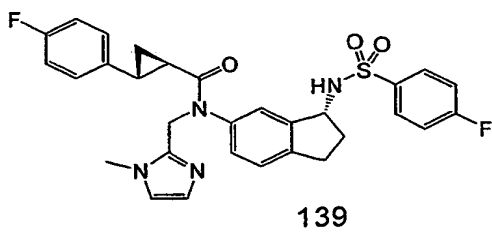
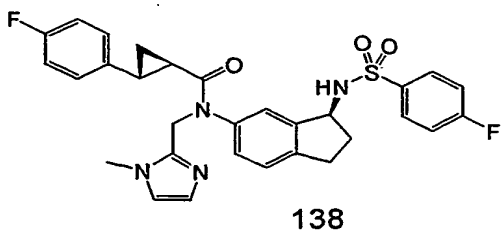
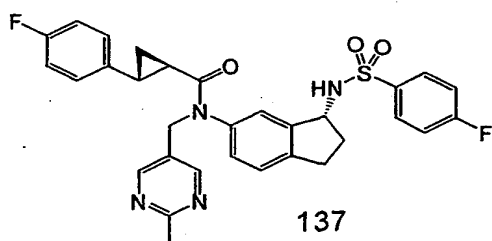
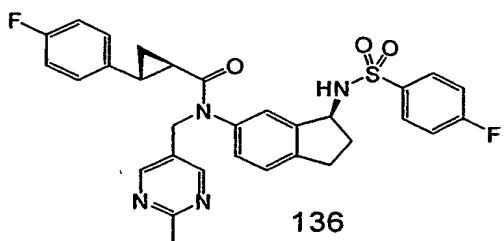
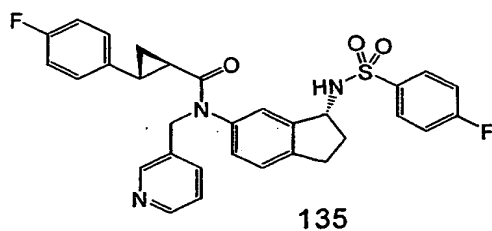
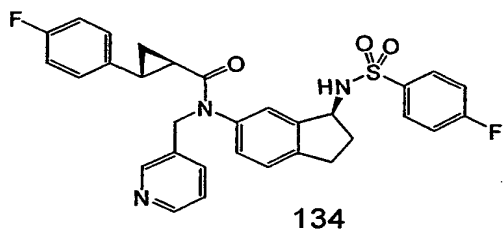
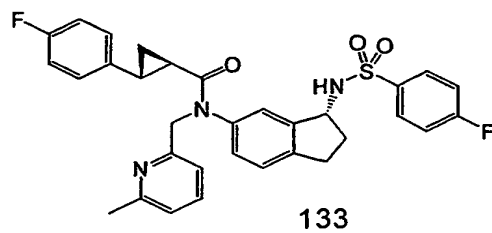
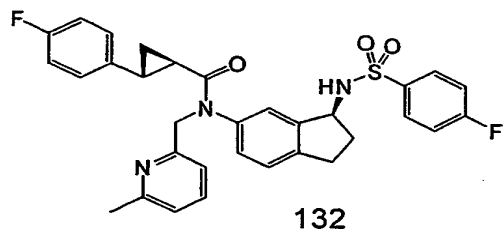
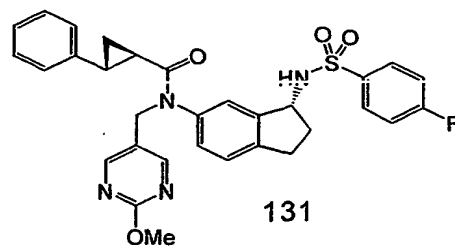
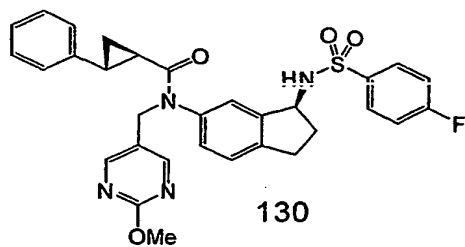
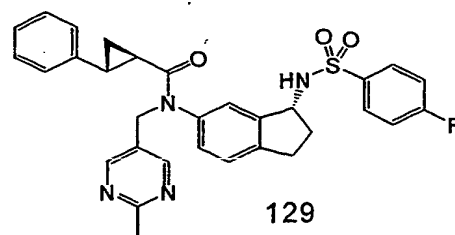
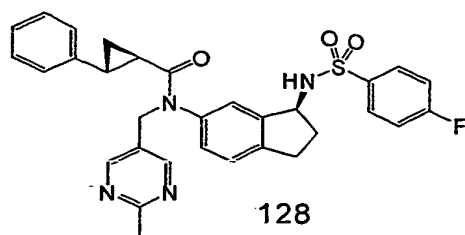


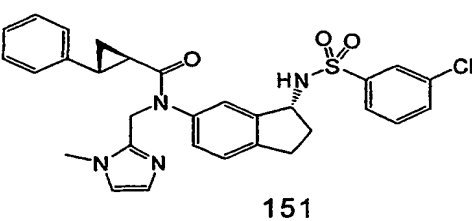
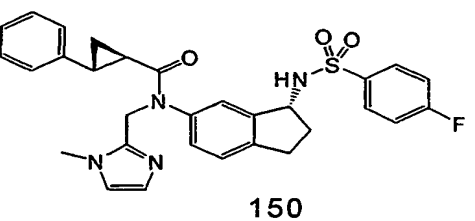
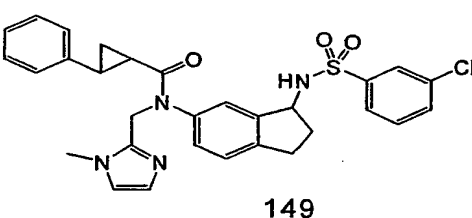
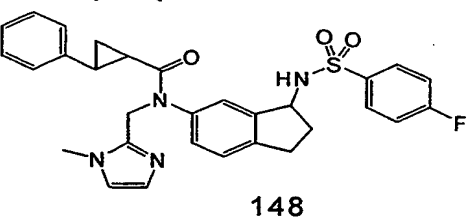
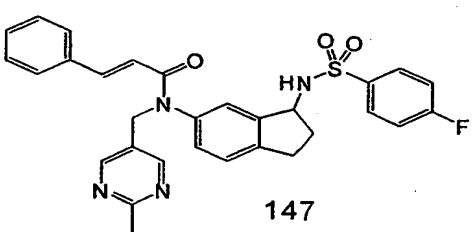
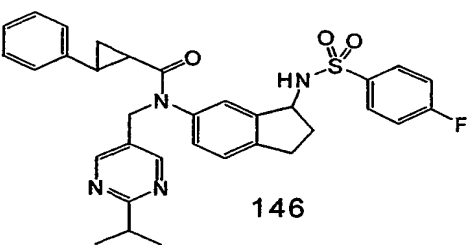
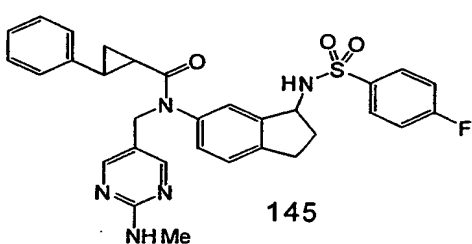
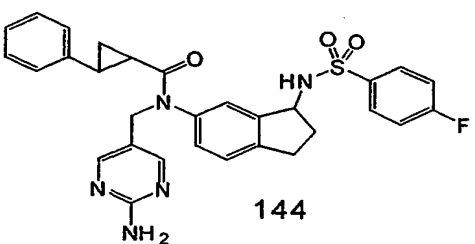
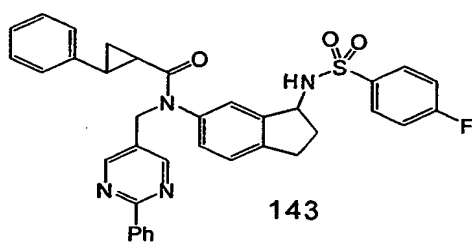
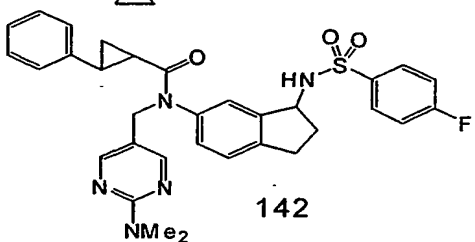
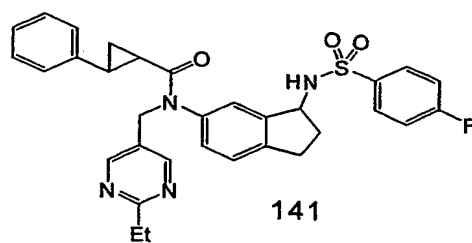
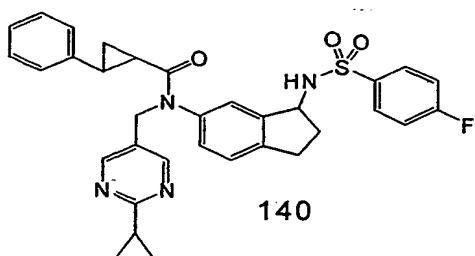


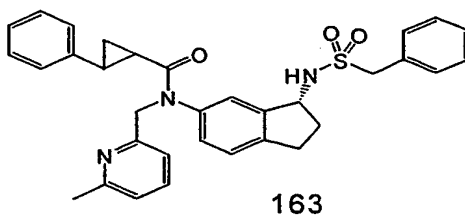
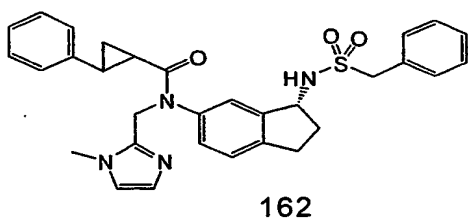
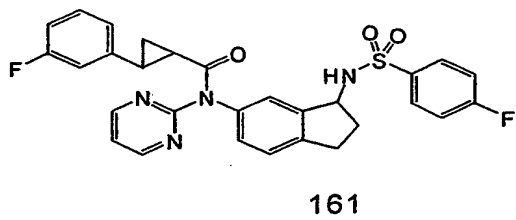
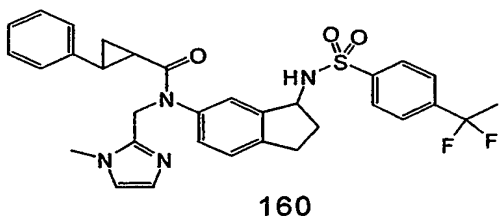
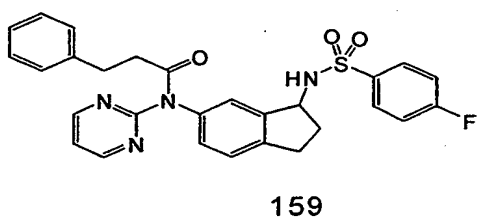
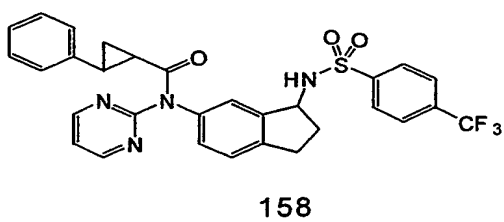
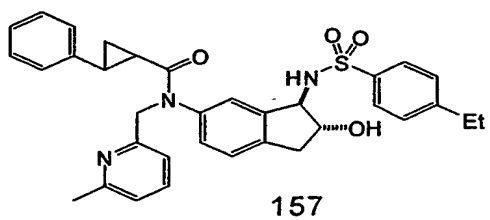
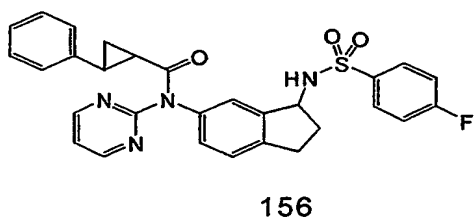
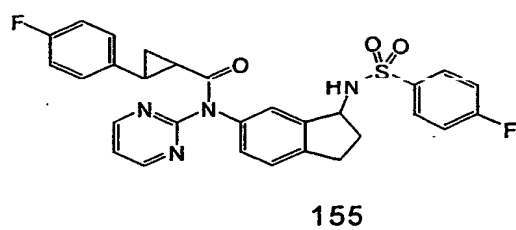
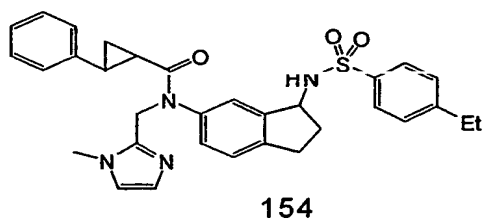
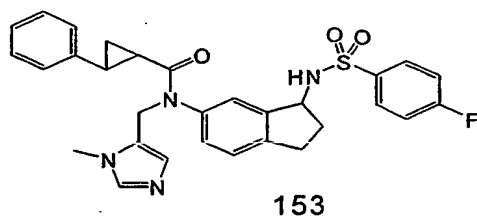
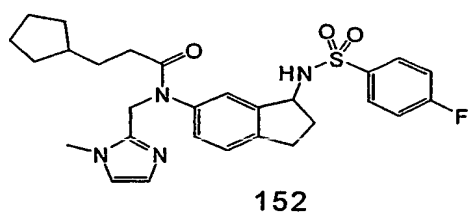


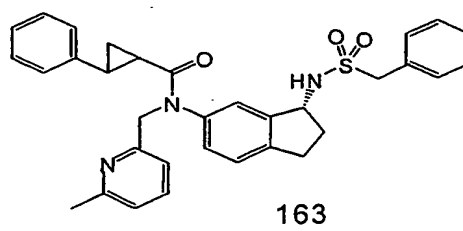
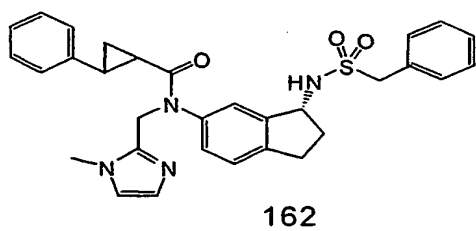
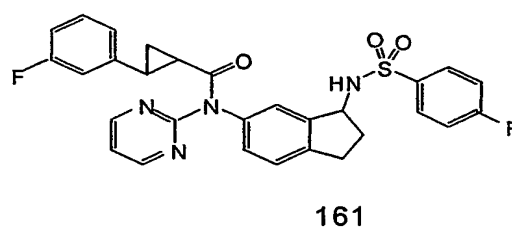
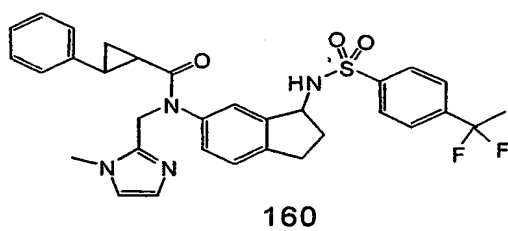
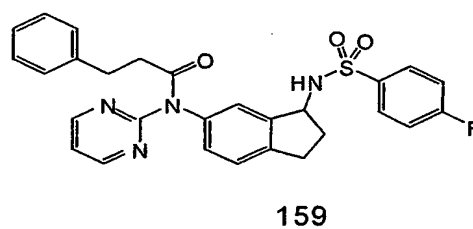
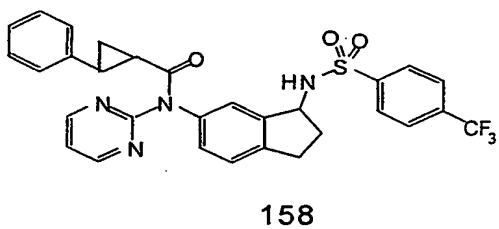
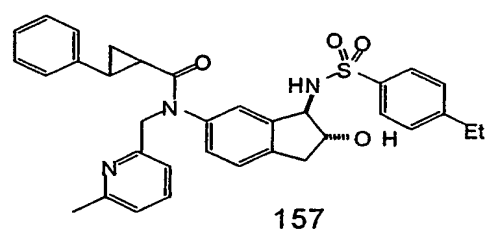
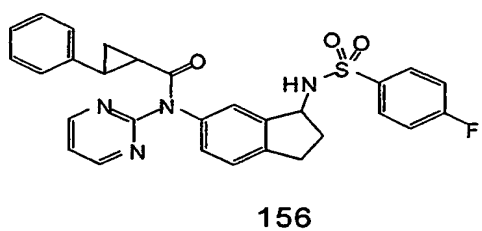
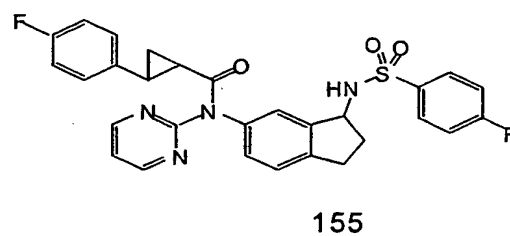
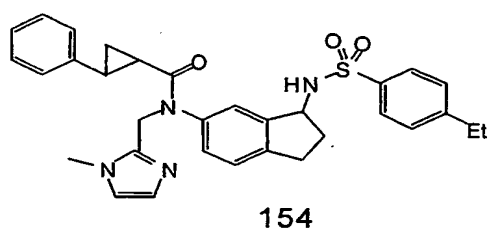
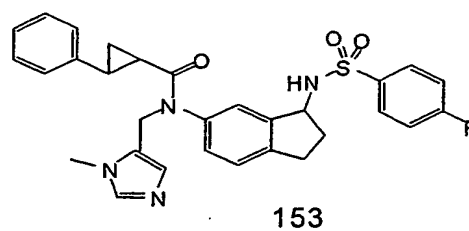
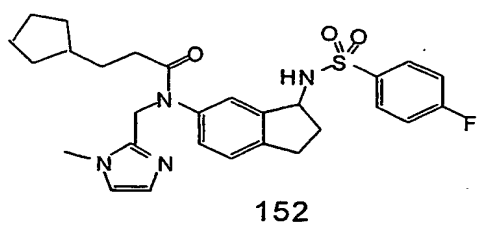


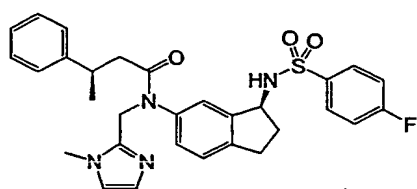




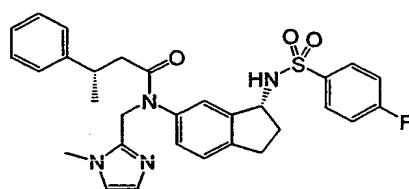




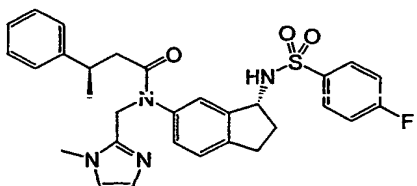




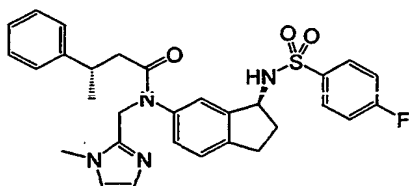
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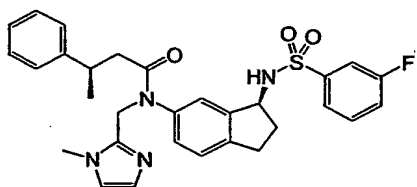
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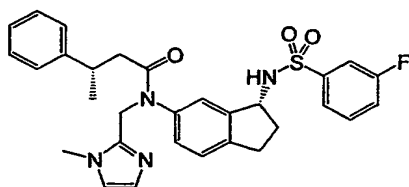
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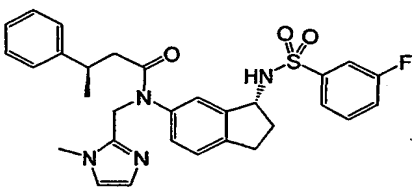
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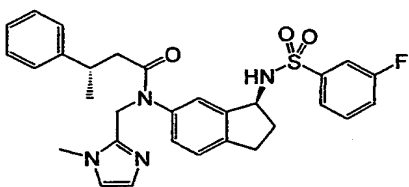
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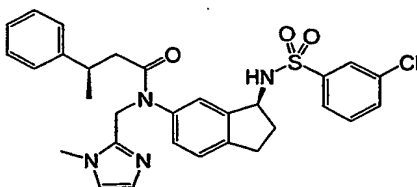
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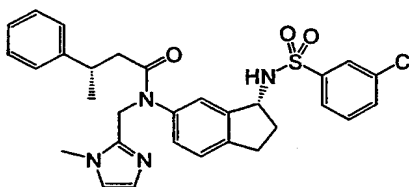
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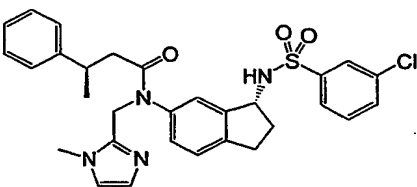
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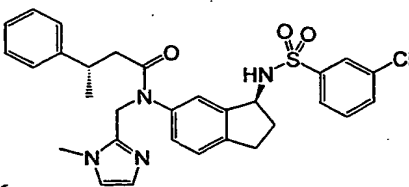
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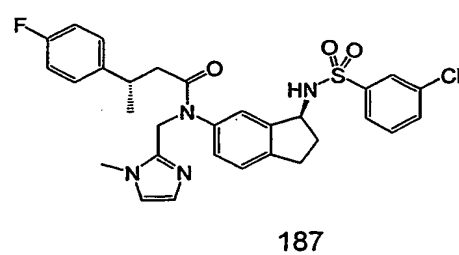
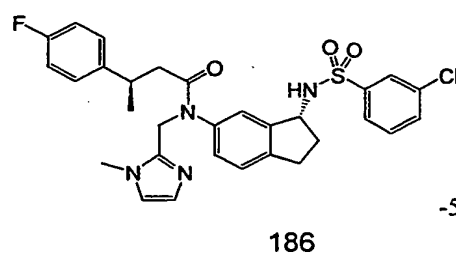
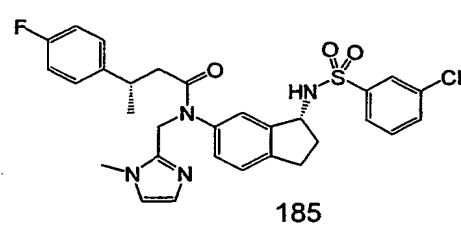
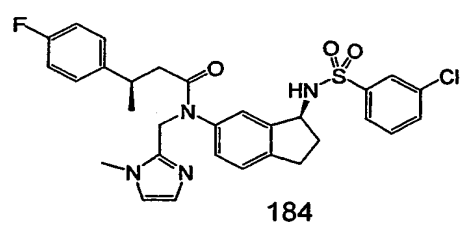
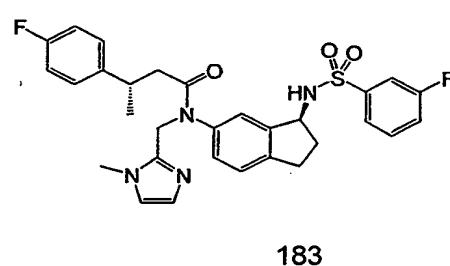
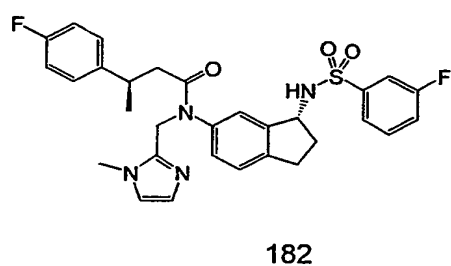
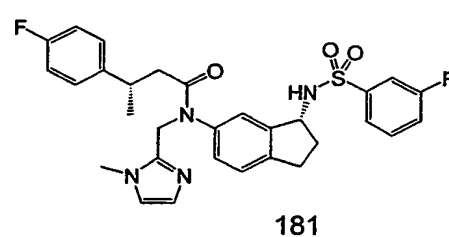
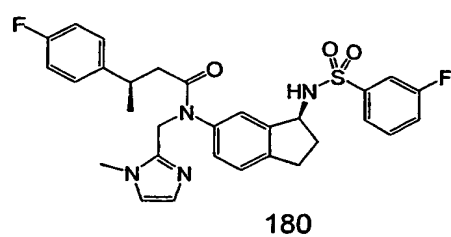
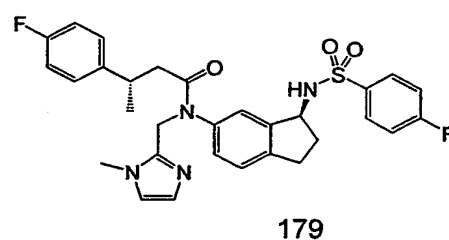
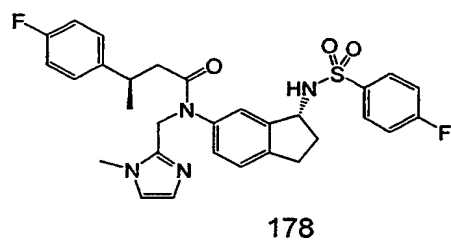
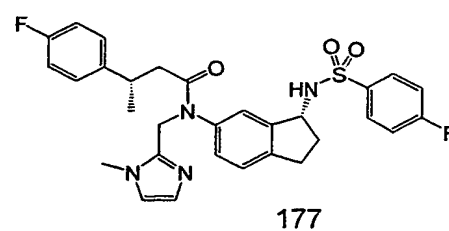
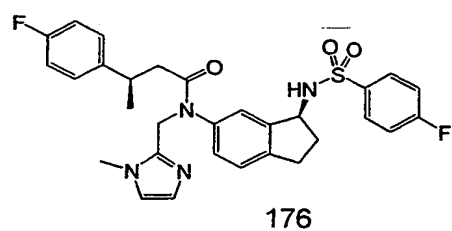
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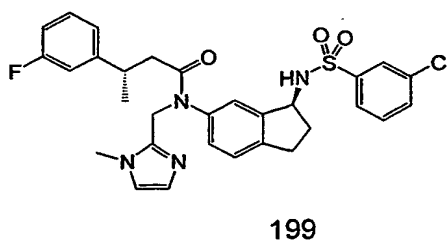
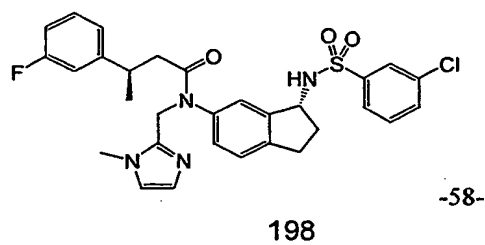
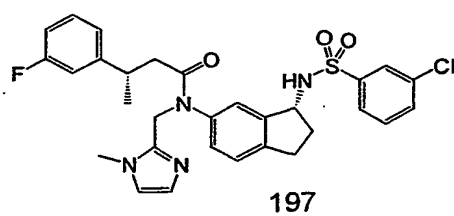
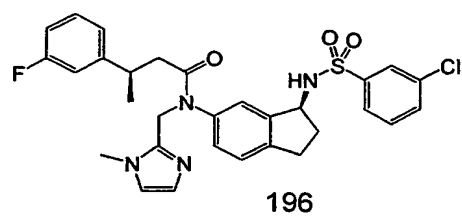
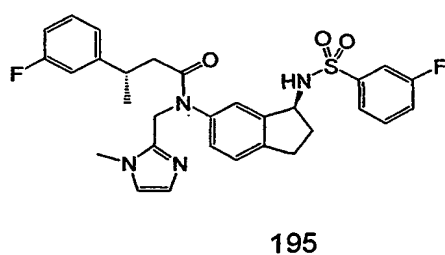
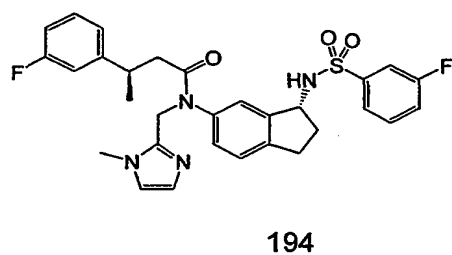
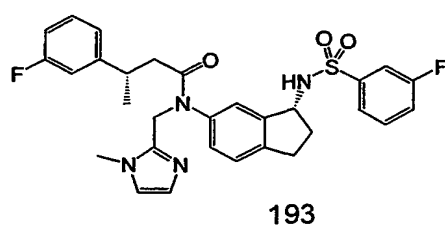
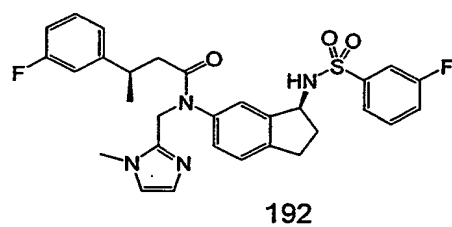
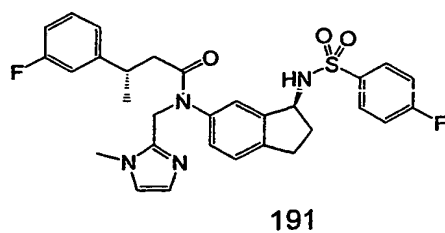
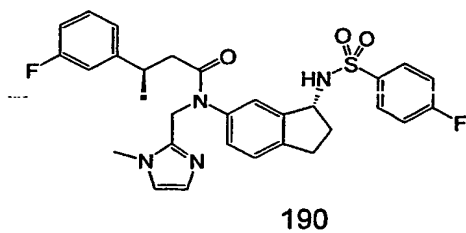
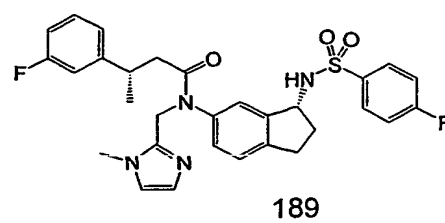
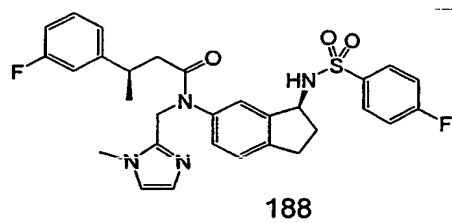


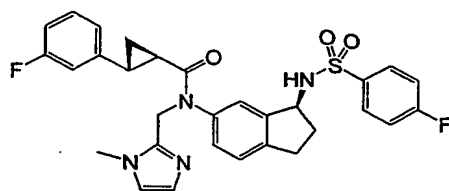
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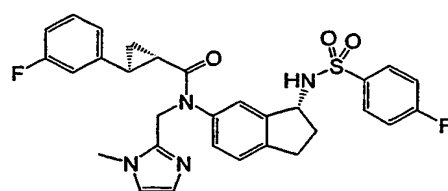
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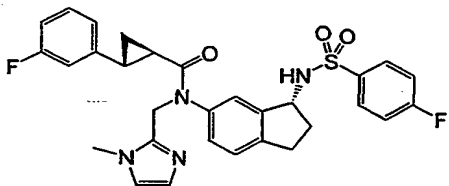




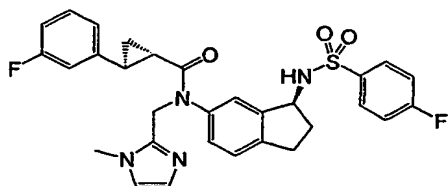
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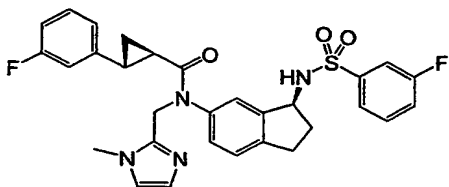
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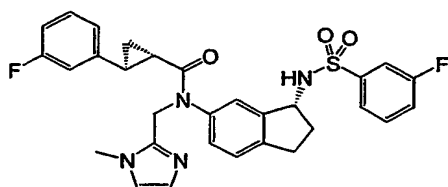
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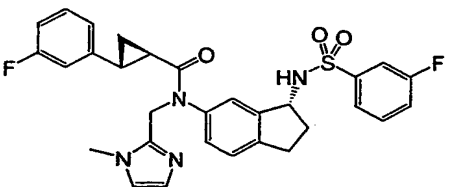
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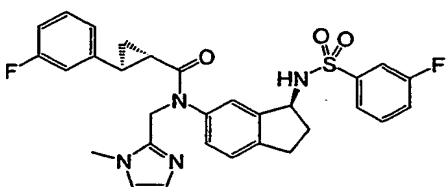
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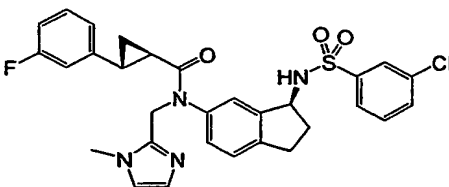
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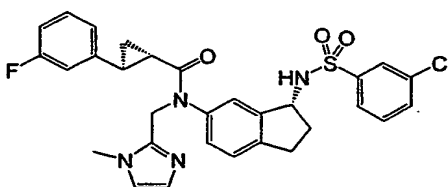
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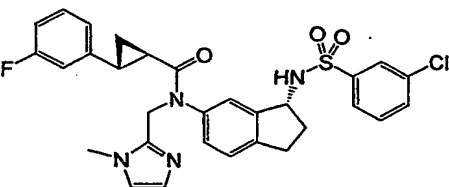
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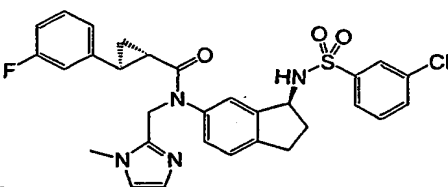
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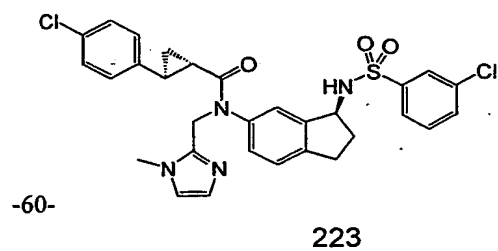
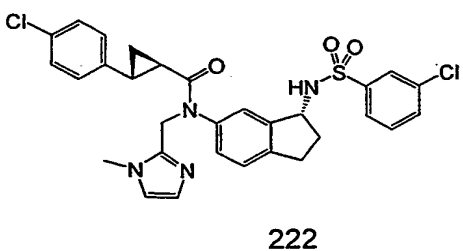
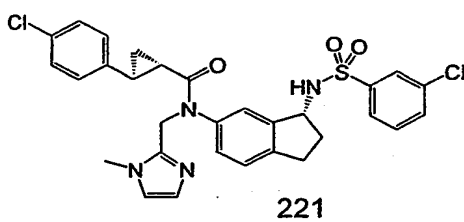
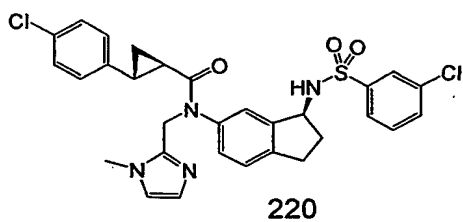
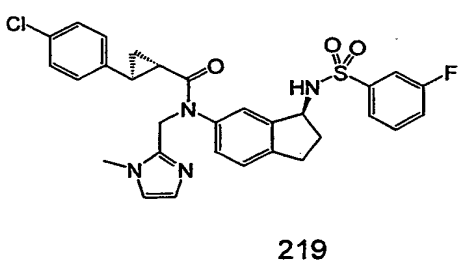
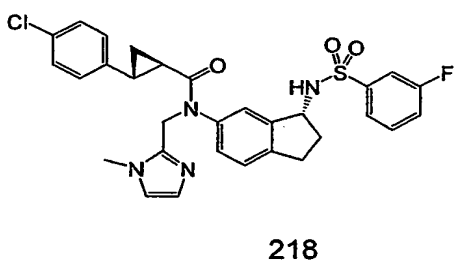
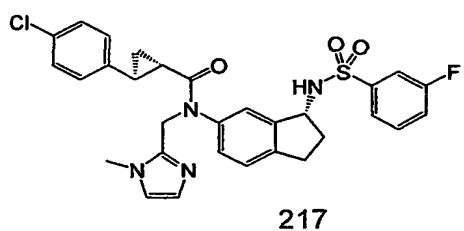
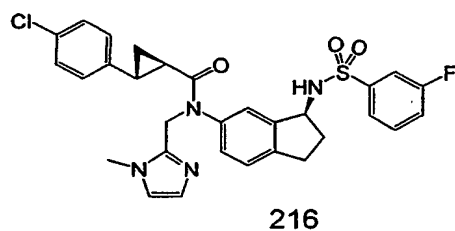
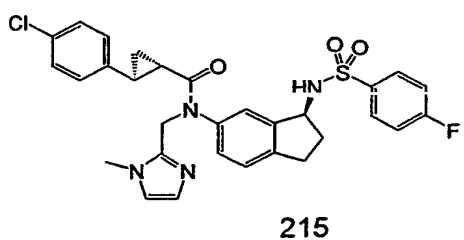
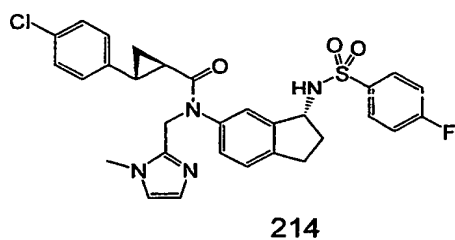
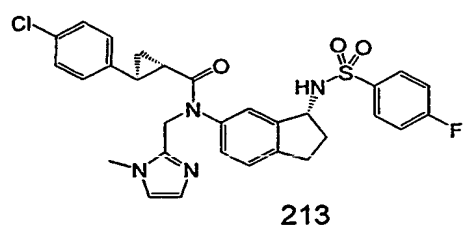
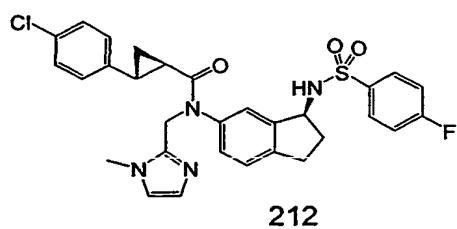
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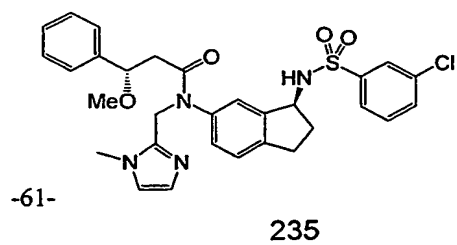
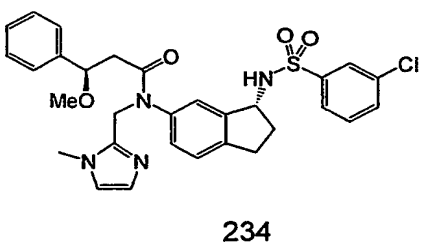
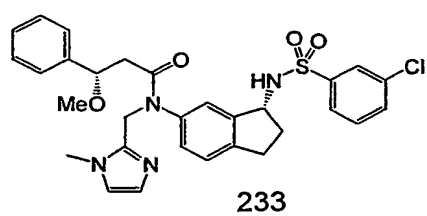
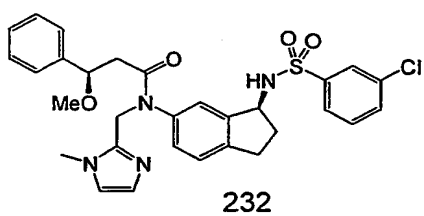
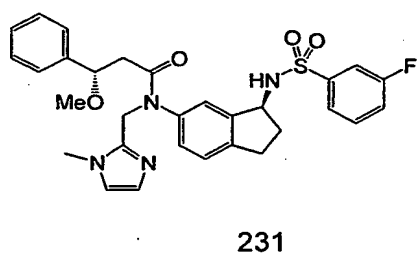
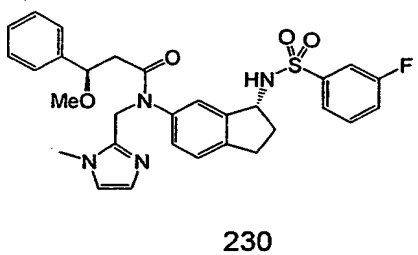
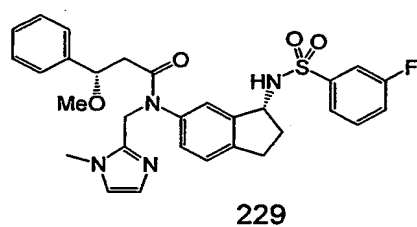
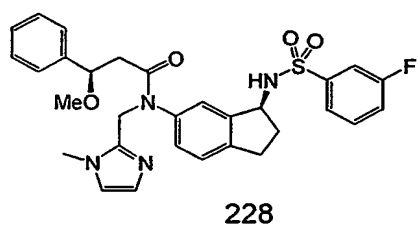
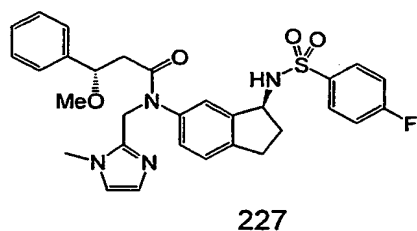
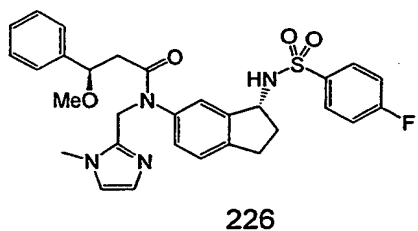
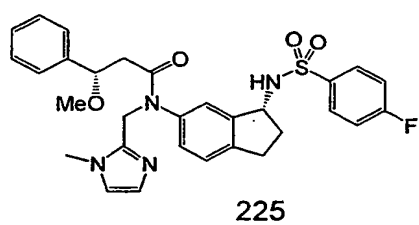
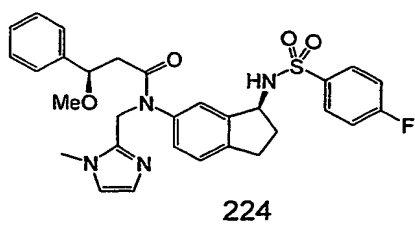


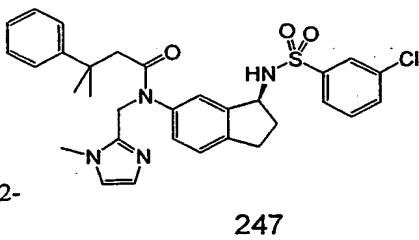
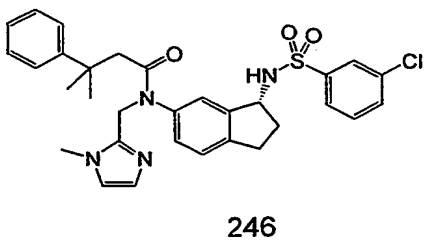
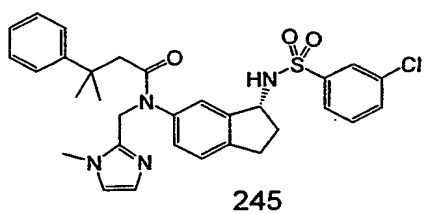
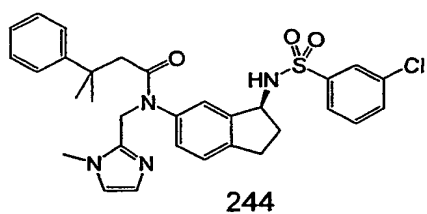
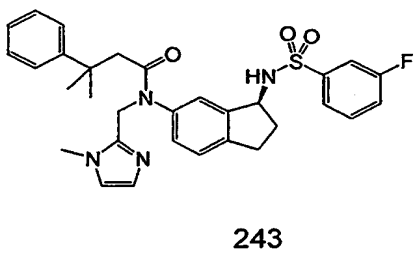
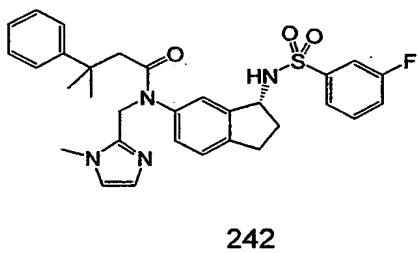
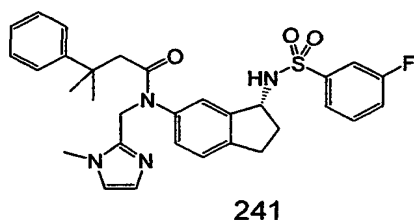
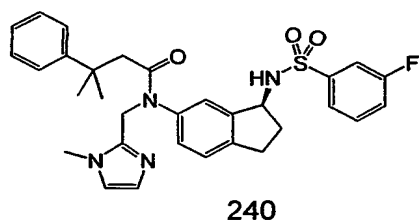
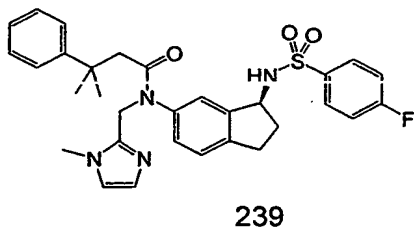
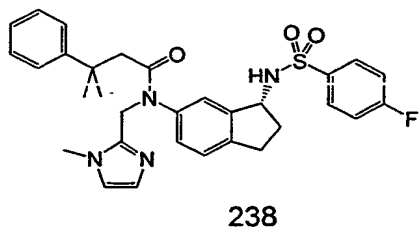
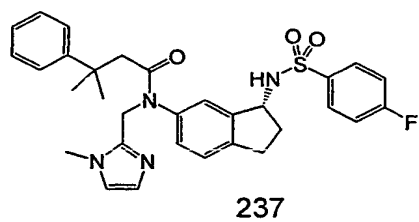
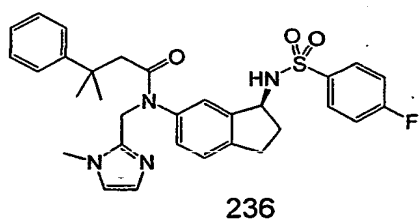
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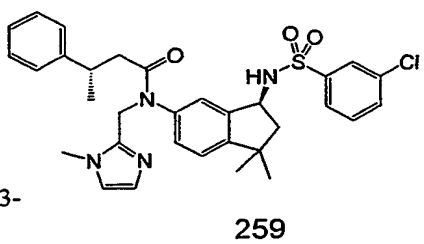
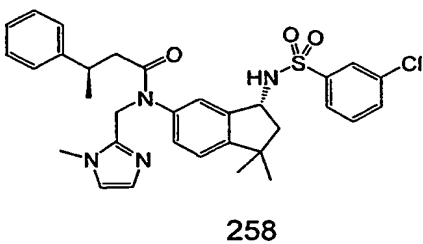
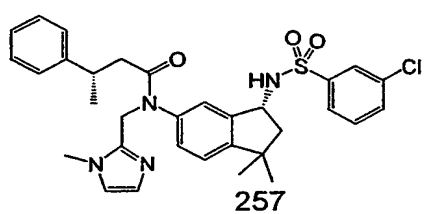
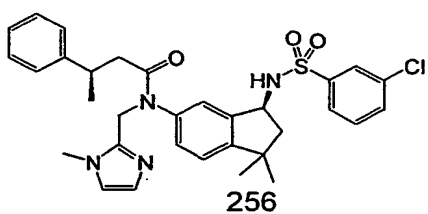
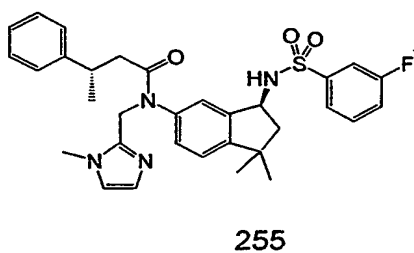
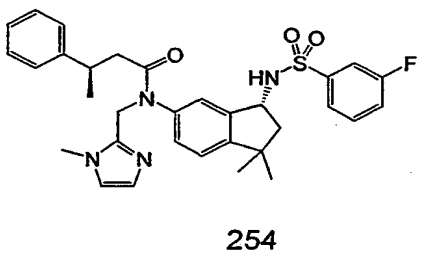
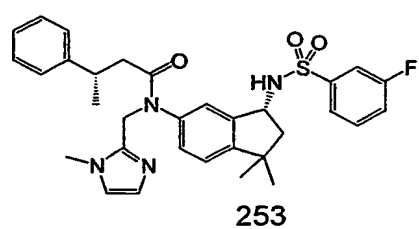
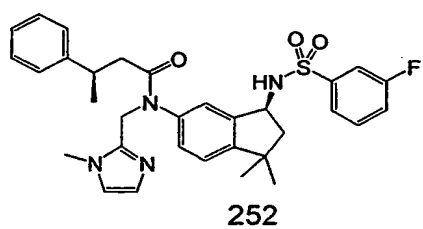
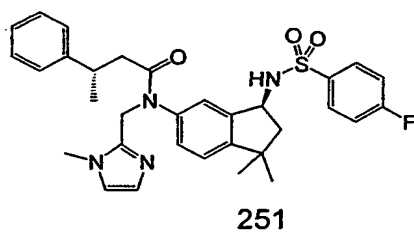
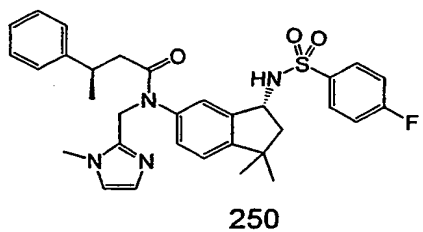
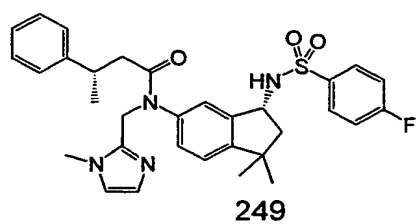
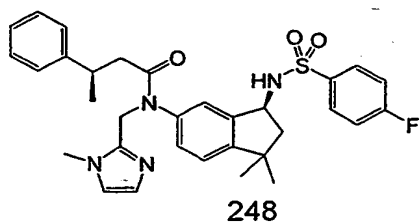


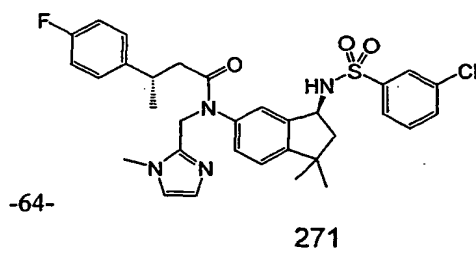
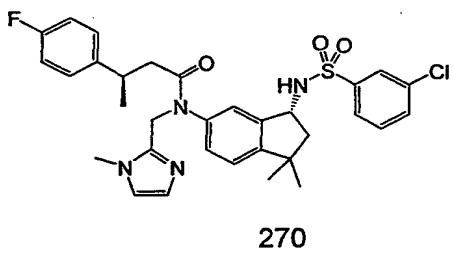
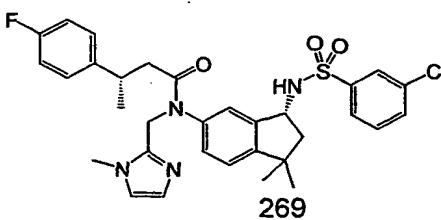
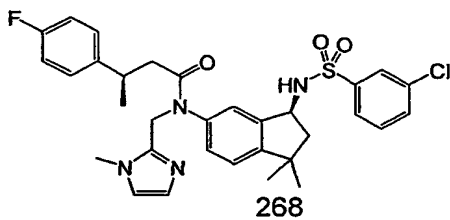
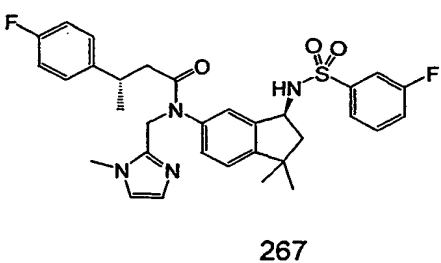
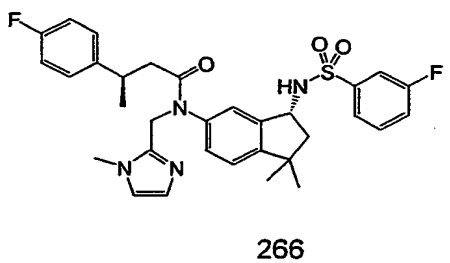
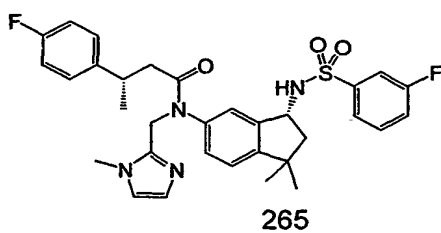
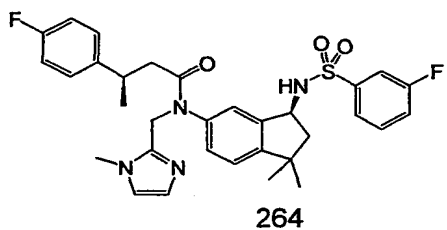
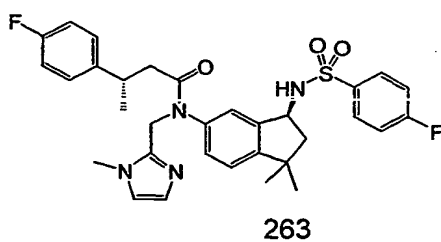
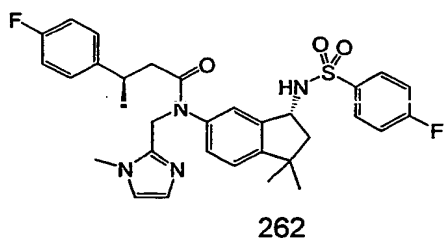
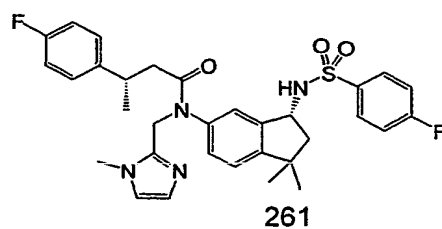
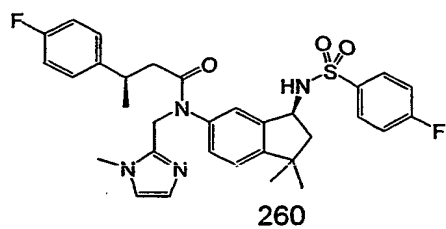
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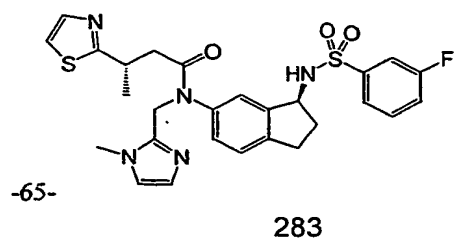
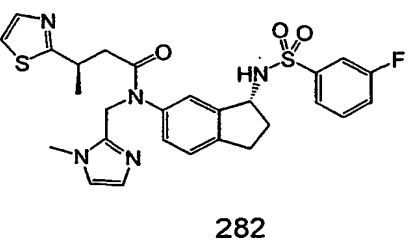
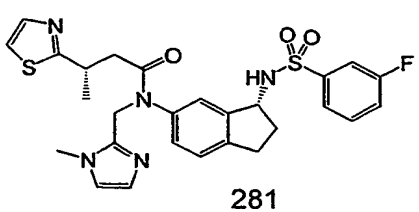
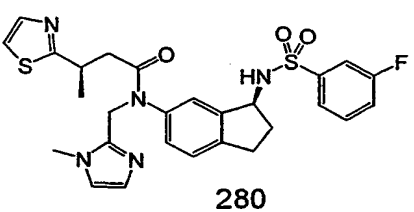
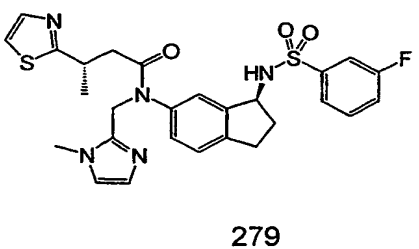
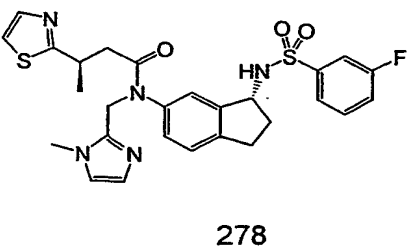
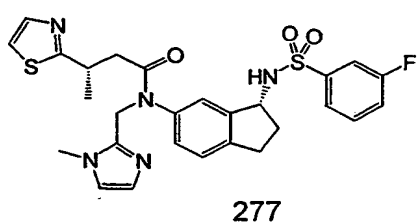
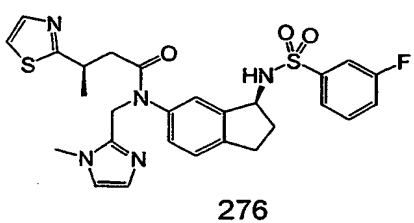
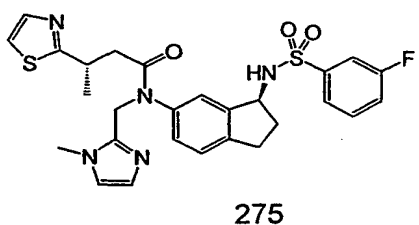
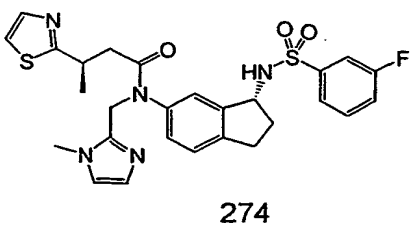
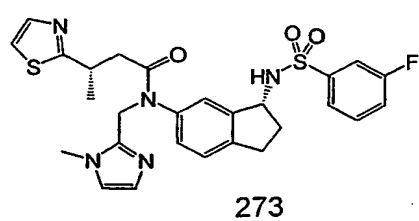
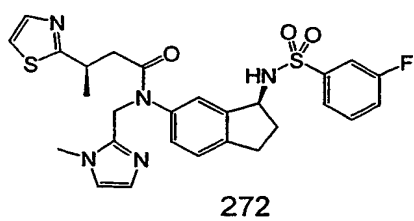


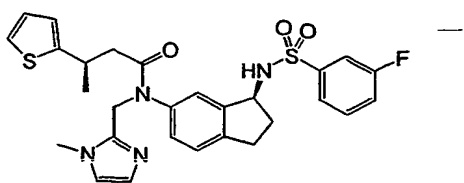




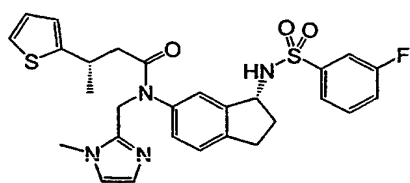




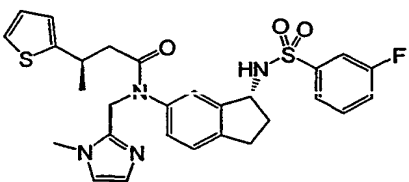




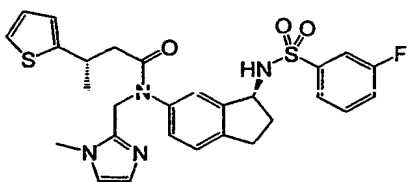
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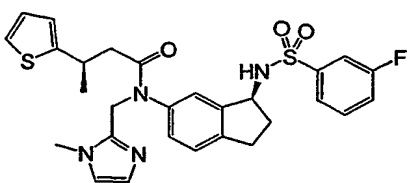
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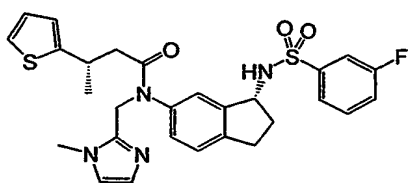
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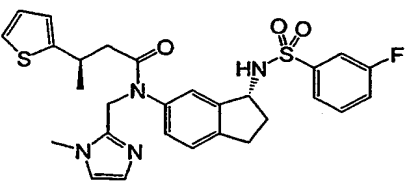
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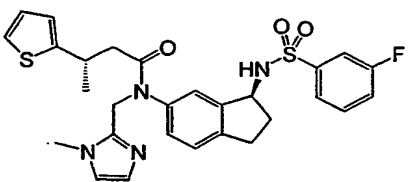
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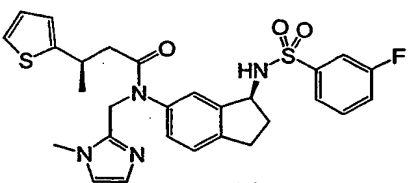
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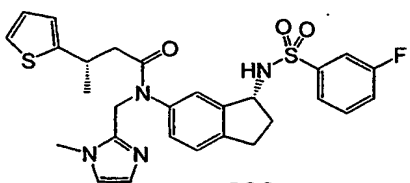
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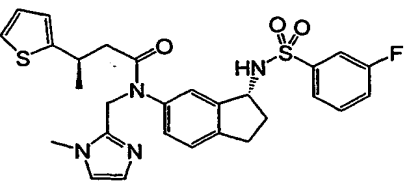
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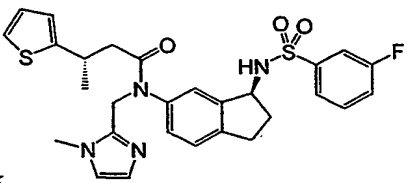
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294

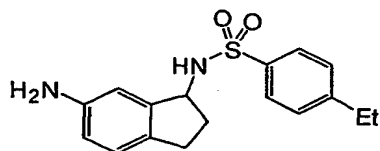


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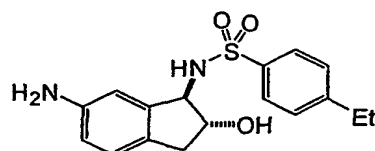
The present invention is further explained in greater detail in the Examples which follow. These experimental examples are intended as illustrative of the invention, and are not to be taken as limiting thereof. Unless otherwise indicated, all references to parts and percentages are based on weight and all temperatures are expressed in degrees Celsius. The scope of the invention is not construed as merely consisting of the following examples.

EXAMPLES

Compound Preparation



97



98

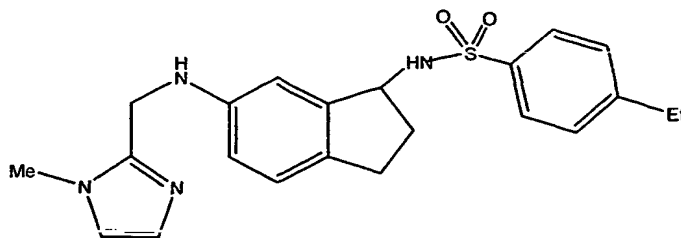
Compounds 97 and 98 and related amino indanes are prepared as described in N. Castle et al W09804521 (See also U.S. 6,083,986 incorporated herein by reference); D. Buckle et al *J Med. Chem.* 1991, 34, 919-926 (and references cited therein) and J. Tedder et al., EP0321175

Separation of the enantiomers of compound 97 and compound 98 can be accomplished by chiral HPLC using a Chiralpak AS column (Chiral Technologies, Inc.) for compound 97 and a Chiralpak OJ column (Chiral Technologies, Inc.) for compound 98. Asymmetric synthetic methods can also be used to separate the enantiomers of compound 97 and compound 98. For example, see N. Castle et al., WO 98/04521 (See also U.S. 6,083,986).

The resolution of racemic *trans*-2-phenylcyclopropanecarboxylic acid to give the (+)-(S) and (-)-(R) isomers is accomplished as described in *Macromolecules*, 1971, 4, 718-719.

Example 1

Preparation of Compound 99



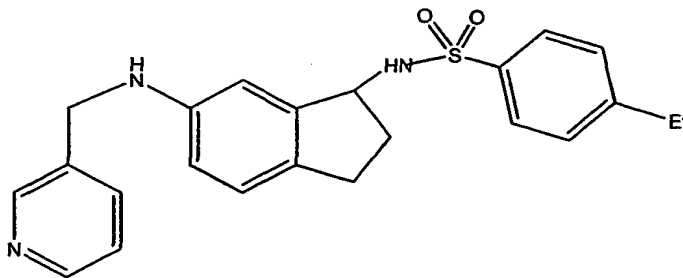
To a stirred solution of Compound 97 (200 mg, 0.948 mmol) in methanol (5 mL) at room temperature was added 1-methyl-2-imidazolecarboxaldehyde (125 mg, 1.13 mmol) and anhydrous sodium sulfate (673 mg, 4.74 mmol). The reaction mixture was heated at 50°C for six hours under nitrogen. The excess sodium sulfate was filtered from the reaction mixture while it was still warm and the filtrate was cooled to room temperature. Sodium borohydride (103 mg, 2.72 mmol) was added to the filtrate and it was stirred for 15 hours at room temperature. The solution was quenched with saturated aqueous sodium bicarbonate solution and the methanol was removed by rotary evaporation. The resulting mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was recrystallized from a minimum amount of hot ethyl acetate to give Compound 99 (229 mg, 59%) as a white solid. The mother liquor was concentrated and subjected to flash column chromatography on silica gel using 9:1 ethyl acetate:methanol as the eluent to provide additional Compound 99 (39 mg). ¹H NMR (300 MHz, d₆-acetone) δ 7.90 (d, 2 H, *J* = 8.2 Hz), 7.47 (d, 2 H, *J* = 8.1 Hz), 6.99 (s, 1 H), 6.92 (d, 1 H, *J* = 8.2 Hz), 6.82 (d, 1 H, *J* = 0.8 Hz), 6.67 (dd, 1 H, *J* = 2.0, 8.1 Hz), 6.50 (s, 1 H), 5.14 (s, 1 H), 4.70 (m, 2H), 4.21 (s, 2H), 3.70 (s, 3H), 2.75, (q 2H, *J* = 7.6 Hz), 2.67 (dd, 1 H, *J* = 3.3, 8.9 Hz), 2.56 (m, 1 H), 2.12 (m, 1 H), 1.69 (m, 1 H), 1.25 (t, 3H, *J* = 7.6 Hz). ¹³C NMR (75 MHz, d₆-acetone) δ 149.4, 147.4, 145.8, 143.4, 139.4, 131.5, 128.3, 126.9, 125.6,

124.6, 121.8, 113.5, 108.1, 58.7, 40.4, 34.2, 31.9, 28.5, 28.3, 14.3.

The following compounds in Example 2 and Example 3 were synthesized using the procedures described in Example 1 using Compound 97 and the appropriate aldehyde.

Example 2

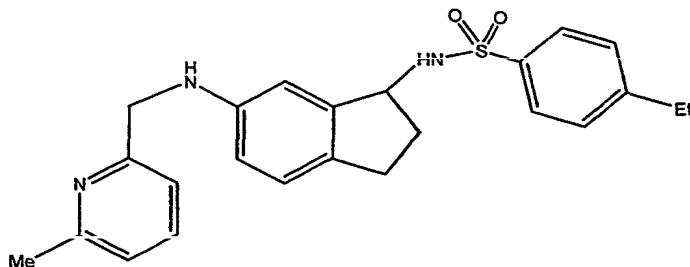
Preparation of Compound 100



Compound 100 was obtained by reacting Compound 97 with 3-pyridine carboxaldehyde under the reaction conditions described in Example 1 in 78% yield. Purification was accomplished by flash column chromatography on silica gel using 6:2:2 ethyl acetate:dichloromethane:hexanes as the eluent. ^1H NMR (300 MHz, CDCl_3) δ 8.47 (s, 1 H), 8.45 (d, $J = 4.8$ Hz, 1 H), 7.81 (d, $J = 8.1$ Hz, 2H), 7.63 (d, $J = 7.8$ Hz, 1 H), 7.31 (d, $J = 8.1$ Hz, 2 H), 7.26-7.20 (m, 1 H), 6.94 (d, $J = 8.1$ Hz, 1 H), 6.45 (d, $J = 7.8$ Hz, 1 H), 6.41 (s, 1 H), 5.43 (s, $J = 9.0$ Hz, 1 H), 4.73 (q, $J = 7.8$ Hz, 1 H), 4.19 (s, 2H), 2.78-2.54 (m, 4H), 2.30-2.20 (m, 1 H), 1.73-1.61 (m, 1 H), 1.23 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 149.5, 149.0, 148.6, 147.0, 143.6, 138.7, 135.4, 134.9, 132.1, 128.6, 127.2, 125.4, 123.6, 113.6, 108.4, 58.9, 46.0, 35.0, 29.1, 28.8, 15.2

Example 3

Preparation of Compound 101

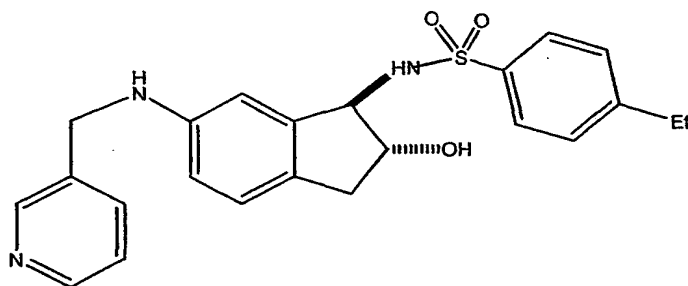


Compound 101 was obtained by reacting Compound 97 with 6-methyl-2-pyridine carboxaldehyde under the reaction conditions described in Example 1 in 66% yield.

Purification was accomplished by recrystallization from ethyl acetate/hexane. ^1H NMR (300 MHz, CDCl_3) δ 7.81 (d, $J = 7.8$ Hz, 2 H), 7.50 (t, $J = 7.8$ Hz, 1 H), 7.31 (d, $J = 7.8$ Hz, 2H), 7.06 (d, $J = 7.02$ (d, $J = 7.8$ Hz, 1 H), 6.92 (d, $J = 8.4$ Hz, 1 H), 6.50 (d, $J = 7.8$, 1 H), 6.38 (s, 1 H), 5.10 (d, $J = 8.7$ Hz, 1 H), 4.72 (q, $J = 7.5$ Hz, 1 H), 4.24 (s, 2 H), 2.70 (q, $J = 7.2$ Hz, 2H), 2.63-2.56 (m, 2H), 2.56 (s, 3H), 2.25-2.22 (m, 1H), 1.71-1.62 (m, 1H), 1.24 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.0, 157.5, 149.4, 147.4, 143.3, 138.6, 136.9, 131.4, 128.6, 127.3, 125.2, 121.7, 118.7, 113.8, 108.3, 58.9, 49.4, 35.0, 29.1, 28.8, 24.5, 15.2

Example 4

Preparation of Compound 102

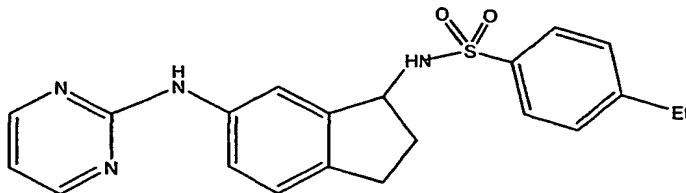


To a stirred solution of Compound 98 (294 mg, 0.88 mmol) in methanol (10

mL) at room temp was added 3-pyridine carboxaldehyde (0.12 mL, 1.27 mmol) followed by anhydrous sodium sulfate (480 mg, 3.38 mmol).). The reaction mixture was heated at 55°C for 24 hours under nitrogen at which time TLC analysis indicated that no starting material remained. The reaction was cooled to 0°C and treated with sodium borohydride (53 mg, 1.40 mmol) in one portion. After 15 minutes at 0°C the cooling bath was removed and the reaction was stirred at room temperature for three hours. The methanol was removed by rotary evaporation and the residue was treated with ethyl acetate and water. The organic layer was separated, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography on silica gel using 8:1:1 ethyl acetate:hexane:acetonitrile as the eluent to provide Compound 102 (197 mg, 53%) as a white foam. ¹H NMR (300 MHz, CDCl₃) δ 8.41 (s, 1 H), 8.33 (d, *J* = 4.2 Hz, 1 H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.16 (dd, *J* = 4.8 and 7.5 Hz, 1 H), 6.86 (d, *J* = 8.1 Hz, 1 H), 6.59 (d, *J* = 7.8 Hz, 1 H), 6.41 (d, *J* = 6.9 Hz, 1 H), 6.20 (s, 1 H), 3.95 (t, *J* = 6.9 Hz, 1 H), 4.30 (q, *J* = 7.5 Hz, 1 H), 4.11 (s, 2H), 3.92 (broad s, 1 H), 3.01 (dd, *J* = 7.5 and 15.3 Hz, 1 H), 2.67-2.60 (m, 3H), 1.19 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 149.7, 148.7, 148.2, 147.3, 140.2, 137.6, 135.5, 135.1, 128.7, 128.3, 127.4, 125.7, 123.7, 113.7, 108.2, 80.8, 65.6, 45.8, 37.0, 28.8, 15.2

Example 5

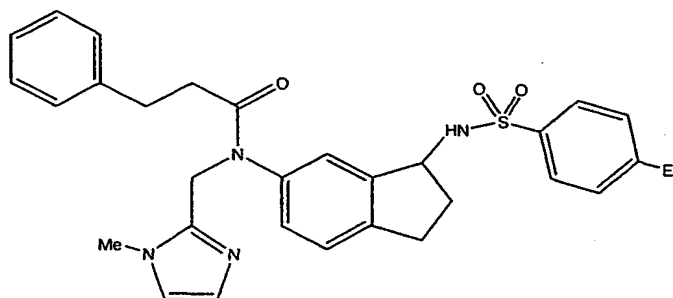
Preparation of Compound 103



To a solution of Compound 97 (100 mg, 0.32 mmol) in 1-methyl-2-pyrrolidinone (0.7 mL) at room temperature was added 2-chloropyrimidine (40 mg, 0.35 mmol). The reaction mixture was heated at 140°C for 21 hours. The crude reaction mixture was directly subjected to flash column chromatography on silica gel eluting with hexane:ethyl acetate (3:2 then 1:1) to give Compound 103 (49 mg, 39%) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 8.33 (2 H, d, J=4.9 Hz), 7.87 (2 H, d, J=8.3 Hz), 7.40 (1 H, dd, J=1.9, 8.0), 7.33 (2 H, d, J=8 Hz), 7.31 (1 H, s), 7.14 (1 H, d, J=8.2 Hz), 6.69 (1 H, t, J=4.8), 5.18 (1 H, d, J=8.9 Hz), 4.83 (1 H, q, J=8.4 Hz), 2.91-2.81 (1 H, m), 2.74-2.64 (1 H, m), 2.71 (2 H, q, J=7.7 Hz), 2.41-2.31 (1 H, m), 1.87-1.72 (2 H, m), 1.25 (3 H, t, J=7.7 Hz).

Example 6

Preparation of Compound 10

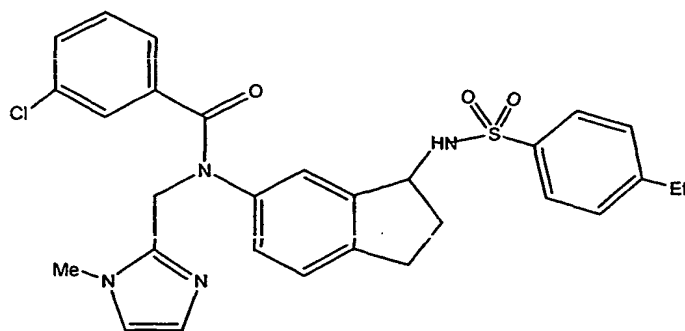


To a stirred solution of Compound 99 (65 mg, 0.16 mmol) in anhydrous THF (1.5 mL) at room temperature was added triethylamine (0.027 mL, 0.20 mmol) followed by hydrocinnamoyl chloride (29 mg, 0.17 mmol). The reaction mixture was stirred at room temperature for 6 hours. Saturated aqueous sodium bicarbonate solution was added and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using 10:1:1 ethyl acetate:dichloromethane:hexanes as the eluent to give Compound 10 (59 mg, 69%) as a white foam. ^1H NMR (300 MHz, d_6 -acetone) δ 7.87 (d, 2H, $J = 8.4$ Hz), 7.48 (d, 2H, $J = 8.2$ -Hz), 7.26 (m, 4H), 7.15 (d, 1 H, $J = 7.2$ Hz), 7.08 (d, 2H, $J = 7.7$ Hz), 6.94 (s, 1 H), 6.76 (d, 1 H, $J = 7.8$ Hz), 6.65 (d, 1 H, $J = 7.8$ Hz), 4.92 (m, 1 H), 4.77 (m, 2 H), 3.59 (s, 3 H), 2.81 (q, 2 H, $J = 6.9$ Hz), 2.74 (m, 4H), 2.24 (m, 3H), 1.76 (m, 1H), 1.26 (t, 3H, 7.6 Hz). ^{13}C NMR (75 MHz, d_6 -acetone) δ 170.8, 149.2, 144.2, 143.7, 142.8, 141.5, 140.0, 128.6, 128.4, 128.3, 128.3, 127.2, 126.9, 125.9, 125.2, 124.3, 121.6, 58.3, 35.8, 34.4., 32.2, 31.2, 29.8, 28.4, 14.8.

The following compounds in Example 7 to Example 10 were synthesized using the procedures described in Example 6 using Compound 99 and the appropriate acid chloride.

Example 7

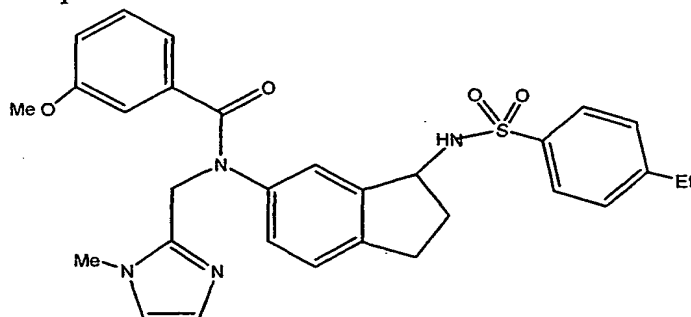
Preparation of Compound 37



Compound 37 was obtained by reacting Compound 99 with 3-chlorobenzoyl chloride in the presence of triethylamine as described in Example 6 in 67% yield. Purification was accomplished by flash column chromatography using EtOAc as the eluent. ^1H NMR (300 MHz, d_6 -acetone) δ 7.87 (d, 2 H, $J = 8.2$ Hz), 7.48 (d, 2 H, $J = 8.4$ Hz), 7.26 (m, 1 H), 7.14 (m, 1 H), 7.08 (d, 1 H, $J = 8.7$ Hz), 7.00 (s, 1 H), 6.96 (d, 1 H, $J = 8.0$ Hz), 6.86 (d, 1 H, $J = 11.1$ Hz), 6.79 (s, 1 H), 5.11 (d, 1 H, $J = 15.2$ Hz), 4.94 (d, 1 H, $J = 15.2$ Hz), 4.69 (m, 1 H), 3.75 (s, 3H), 2.77 (q, 2H, $J = 7.7$ Hz), 2.72 (m, 1 H), 2.63 (m, 1 H), 2.22 (m, 1 H), 1.72 (m, 1H) 1.27 (t, 3H, 7.7 Hz). ^{13}C NMR (75 MHz, d_6 -acetone) δ 167.9, 149.2, 144.1, 143.6, 141.9, 141.5, 139.9, 138.5, 133.2, 129.4, 129.3, 128.6, 128.4, 128.3, 127.2, 127.1, 126.9, 124.8, 123.8, 121.6, 58.3, 45.2, 34.5, 32.3, 14.8.

Example 8

Preparation of Compound 45

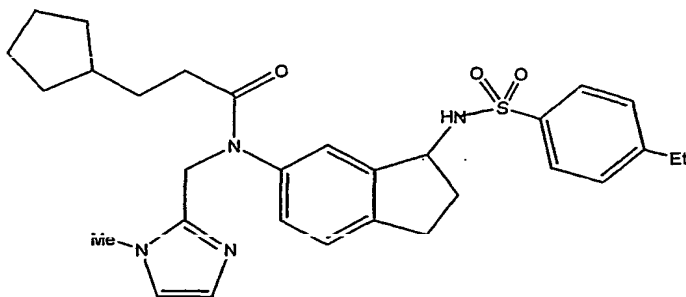


Compound 45 was obtained by reacting Compound 99 with m-anisoyl chloride in the presence of triethylamine as described in Example 6 in 90% yield.

Purification was accomplished by flash column chromatography using 10:1 ethyl acetate:hexanes as the eluent. ^1H NMR (300 MHz, d_6 -acetone) δ 7.89 (d, 2H, $J = 8.2$ Hz), 7.48 (d, 2H, $J = 8.2$ Hz), 7.24 (d, 1H, $J = 8.6$ Hz), 7.07 (t, 1H, $J = 8.0$ Hz), 7.01 (s, 1H), 6.91 (d, 1H, $J = 8.0$ Hz), 6.79 (m, 5H), 5.16 (d, 1H, $J = 15.1$ Hz), 4.92 (d, 1H, $J = 15.2$ Hz), 4.68 (dd, 1H, $J = 7.8, 15.8$ Hz), 3.77 (s, 3H), 3.63 (s, 3H), 2.76 (q, 2H, $J = 7.7$ Hz), 2.71 (dd, 1H, $J = 3.1, 8.4$ Hz), 2.63 (m, 1H), 2.24 (m, 1H), 1.73 (m, 1H), 1.26 (t, 3H, $J = 7.6$ Hz).

Example 9

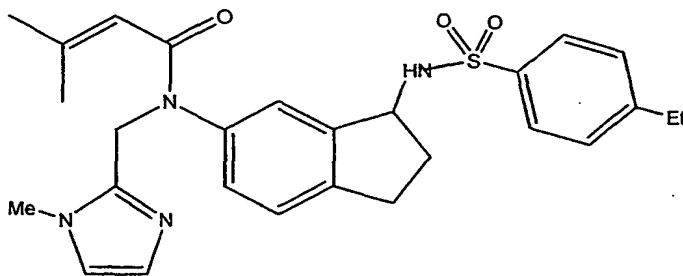
Preparation of Compound 46



Compound 46 was obtained by reacting Compound 99 with 3-cyclopentylpropionyl chloride in the presence of triethylamine as described in Example 6 in 44% yield. Purification was accomplished by flash column chromatography using 10:1 ethyl acetate:hexanes as the eluent. ^1H NMR (300 MHz, d_6 -acetone) δ 7.89 (d, 2H, $J = 8.1$ Hz), 7.45 (d, 2H, $J = 8.2$ Hz), 7.28 (m, 1H), 7.13 (d, 1H, $J = 8.0$ Hz), 6.97 (s, 1H), 6.91 (d, 1H, $J = 8.0$ Hz), 6.89 (d, 1H, $J = 6.7$ Hz), 6.68 (d, 1H, $J = 14.8$ Hz), 4.94 (d, 1H, $J = 15.0$ Hz), 4.78 (m, 2H), 3.68 (s, 3H), 2.88 (m, 4H), 2.76 (q, 2H, $J = 7.5$ Hz), 2.70 (m, 1H), 2.29 (m, 1H), 1.95 (m, 2H), 1.82 (m, 1H), 1.50 (m, 8H), 1.26 (t, 3H, $J = 7.6$ Hz).

Example 10

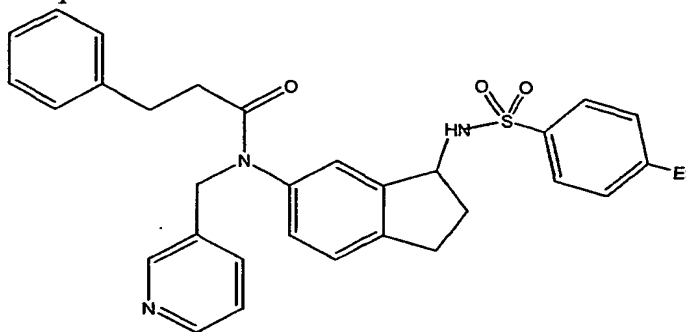
Preparation of Compound 47



Compound 47 was obtained by reacting Compound 99 with 3,3-dimethylacryloyl chloride in the presence of triethylamine as described in Example 6 in 37% yield. Purification was accomplished by flash column chromatography using 10:1 ethyl acetate: hexanes as the eluent. ^1H NMR (300 MHz, d_6 -acetone) δ 7.88 (d, 2H, $J = 8.3$ Hz), 7.44 (d, 2H, $J = 8.4$ Hz), 7.26 (d, 1H, $J = 8.6$ Hz), 7.10 (d, 1H, $J = 7.9$ Hz), 6.96 (s, 1H), 6.89 (d, 1H, $J = 8.0$ Hz), 6.71 (s, 1H), 5.39 (s, 1H), 4.98 (d, 1H, $J = 15.1$ Hz), 4.78 (m, 2H), 3.71 (s, 3H), 2.76 (m, 4H), 2.30 (m, 1H), 2.09 (s, 3H), 1.82 (m, 1H), 1.63 (s, 3H), 1.25 (t, 3H, $J = 7.6$ Hz).

Example 11

Preparation of Compound 2

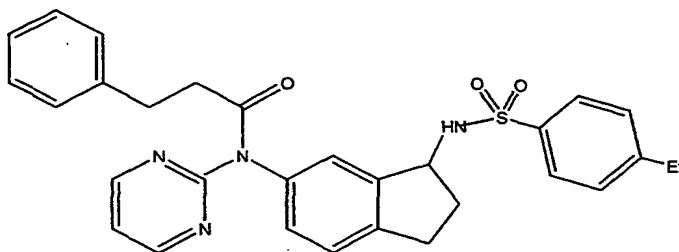


To a stirred solution of Compound 100 (47 mg, 0.12 mmol) in anhydrous tetrahydrofuran (8 mL) at 0°C was added triethylamine (0.03 mL, 0.21 mmol) followed by hydrocinnamoyl chloride (34 mg; 0.20 mmol). The reaction was allowed to stir for 21 hours slowly warming to room temperature. The solvent was removed by rotary evaporation and the residue was treated with ethyl acetate and saturated aqueous sodium chloride solution. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography on silica gel using 8:1:1 ethyl acetate: dichloromethane:acetonitrile as the eluent to give Compound 2 (45 mg, 73%) as a white foam. ^1H NMR (300 MHz, CDCl_3) δ 8.36 (d, $J = 3.6$ Hz, 1H), 8.12 (s, 1H),

7.78 (d, $J = 8.1$ Hz, 2H), 7.53 (d, $J = 7.8$ Hz, 1 H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.22-7.11 (m, 4H), 7.03-7.00 (m, 2H), 6.55 (s, 1H), 6.48 (d, $J = 7.8$ Hz, 1H), 5.91 (d, $J = 9.3$ Hz, 1H), 4.85-4.59 (m, 3H), 2.88-2.59 (m, 6H), 2.30-2.22 (m, 4H), 1.75-1.67 (m, 1 H), 1.25 (t, $J = 7.8$ Hz, 3H) ^{13}C NMR (75 MHz, CDCl_3) δ 172.2, 149.7, 148.5, 144.5, 142.9, 141.0, 140.4, 138.6, 137.0, 133.1, 128.7, 128.6, 128.41, 128.35, 127.2, 126.27, 125.8, 124.1, 123.7, 58.3, 50.4, 36.0, 34.7, 31.7, 29.7, 28.8, 15.2.

Example 12

Preparation of Compound 49



To a stirred solution of Compound 103 (49 mg, 0.13 mmol) in anhydrous tetrahydrofuran (1 mL) at room temperature were added triethylamine (0.028 mL, 0.20 mmol) and hydrocinnamoyl chloride (0.024 mL, 0.16 mmol). After 24 hours, additional triethylamine (0.028 mL, 0.20 mmol) and hydrocinnamoyl chloride (0.024 mL, 0.16 mmol) were added and the reaction mixture was allowed to stir an additional 24 hours. The reaction was diluted with ethyl acetate and the organic layer was washed with saturated aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution. The organic was concentrated and the residue was purified by flash column chromatography on silica gel using 2:1 hexanes:ethyl acetate as the eluent to give Compound 49 (40 mg, 58%) as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ (ppm): 8.63 (2 H, d, $J = 4.9$ Hz), 7.81 (2 H, d,

J=8.3 Hz), 7.31-7.17 (8 H, m), 7.09 (1 H, t, J=4.7 Hz), 7.01 (1 H, dd, J=1.7, 7.9 Hz), 6.91 (1 H, s), 5.02 (1 H, d, J=9 Hz), 4.82 (1 H, q, J=8.0 Hz), 3.06-2.63 (6 H, m), 2.71 (2 H, q, J=7.5 Hz), 2.35-2.25 (1 H, m), 1.78-1.71 (1 H, m), 1.26 (3 H, t, J=7.5 Hz).

¹³C NMR (75 MHz, CDCl₃) δ (ppm): 174.14, 161.34, 158.39, 143.61, 142.62, 141.15, 139.95, 138.31, 128.78, 128.68, 128.59, 128.51, 128.34, 127.27, 126.21, 125.76, 124.34, 117.69, 58.60, 38.67, 35.04, 31.63, 29.86, 28.85, 15.17.

BioAssays

The cloning, construction and testing of CHO cells that express human voltage-gated potassium channels are described in prior U.S. Patent Application 08/893,160 (published as WO 98/04521), as are assays measuring ⁸⁶rubidium efflux from cell monolayers; fluorescence measurement of cell membrane potential; electrophysiological studies and lymphocyte proliferation studies.

The efficacy of various compounds of the present invention as inhibitors of Kv1.5 are shown in Table 1 (using the known patch clamp techniques cited above and described in detail in WO 98/04521, the disclosure of which is incorporated herein by reference.

TABLE 1

<u>Compound</u>	<u>% Inhibition at 0.1 μM (n2)</u>
2	55
4	50
10	53
33	59
37	53
46	35
49	66
75	48
86	55
93	33
94	53
148	58
154	37
157	40

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since they are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention. Those skilled in the art will recognize variations in the processes as described above and will recognize appropriate modifications based on the above disclosure for making and using the compounds of the invention.

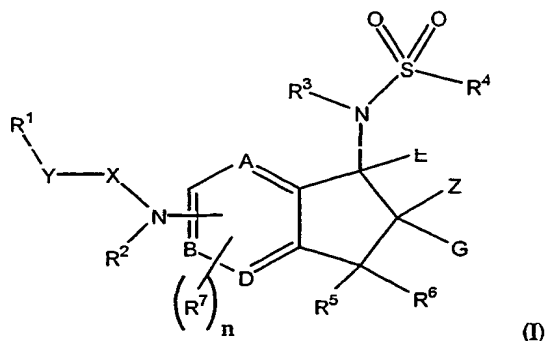
In the forgoing specification, the following abbreviations are used:

<u>Designation</u>	<u>Reagent or Fragment</u>
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
Et	ethyl
NaBH ₄	sodium borohydride
CH ₂ Cl ₂	dichloromethane
SnCl ₂	tin (II) chloride dihydrate
CDCl ₃	chloroform-d

CLAIMS

We claim:

1. A compound having potassium channel inhibitory activity of formula (I), or a pharmaceutically acceptable salt or prodrug thereof:



wherein,

A, B, and D are selected from a substituted carbon atom, a nitrogen atom or N→O, wherein at least one of A, B, and D is a substituted carbon atom and at most only one of A, B and D is N→O;

E and G are each hydrogen, or E and G taken together form a bond;

R¹ is selected from hydrogen, alkyl, carbocycloalkyl, aryl, heterocyclo, heteroaryl, alkoxy, aryloxy, and substituted amino;

Y is selected from a bond, alkyl, carbocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclo;

X is one of C=O, C=S or SO₂;

R² and R³ are independently selected from hydrogen (H), alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, (heteroaryl)alkyl, aminoalkyl; substituted aminoalkyl, carboxyalkyl, alkoxyalkanoyl, aminoalkanoyl, substituted

aminoalkanoyl, alkanoylamidoalkyl, alkanoyl(substituted amido)alkyl, aroylamidoalkyl, aroyl(substituted amido)alkyl, heterocyclocarbonylamidoalkyl, heterocyclocarbonyl(substituted amido)alkyl, heteroaroylamidoalkyl, and heteroaroyl(substituted amido)alkyl;

R^4 is selected from alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heteroaryl and heterocyclo;

R^5 and R^6 are each independently selected from hydrogen and alkyl;

R^7 is independently selected from hydrogen, alkyl, hydroxy, alkoxy, amino, substituted amino, nitro, cyano, halo, carboxy, alkoxycarbonyl, aminocarbonyl, substituted aminocarbonyl and n is 1, 2 or 3;

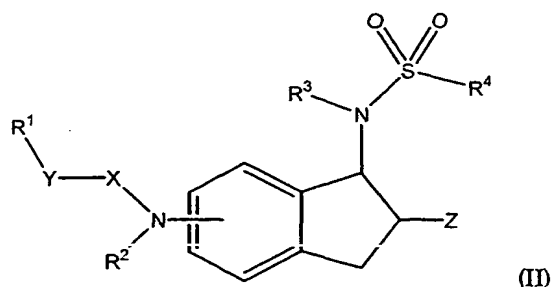
Z is selected from hydrogen, alkyl, hydroxy, SH, alkoxy, aryloxy, alkylthio, amino, substituted amino, alkoxycarbonyl, alkanoylamido, aroylamido, heterocyclocarbonylamido, heteroaroylamido, alkanoyl(alkylsubstituted) amido, aroyl(alkylsubstituted)amido, heteroaroyl(alkylsubstituted)amido, and heterocyclocarbonyl(alkyl substituted)amido;

with the provisos that

i) when R^4 is aryl, then R^4 is not a 3,4-dialkoxy phenyl, or a 3-cycloalkylalkoxy, 4-alkoxy phenyl and

ii) when A, B, and D are all CH, and Z is H, OR^a , or NR^bR^c wherein R^a is one of H, $(CH_2)_m-R^8$ or $C(O)-(CH_2)_m-R^8$, m is 1 to 5, R^8 is $N(R^9)_2$, $N(R^9)_3L$ or CO_2R^9 , each R^9 being independently selected from one of H or alkyl, and L is a counter ion, R^b is H or alkyl; R^c is H, alkyl, or CO_2R^{10} , and R^{10} is alkyl; then when R^2 is hydrogen, or methyl, R^3 is not hydrogen, or alkyl, and when R^3 is H, or alkyl then R^2 is not H, or methyl.

2. A compound having potassium channel inhibitory activity of formula (II), or a pharmaceutically acceptable salt or prodrug thereof



wherein

R¹ is selected from hydrogen, alkyl, carbocycloalkyl, aryl, heterocyclo, heteroaryl, alkoxy, aryloxy, and substituted amino;

Y is selected from a bond, alkyl, carbocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclo;

X is one of C=O, C=S or SO₂;

R² and R³ are independently selected from hydrogen, alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, (heteroaryl)alkyl, aminoalkyl; substituted aminoalkyl, carboxyalkyl, alkoxyalkanoyl and aminoalkanoyl;

R⁴ is selected from alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heteroaryl and heterocyclo;

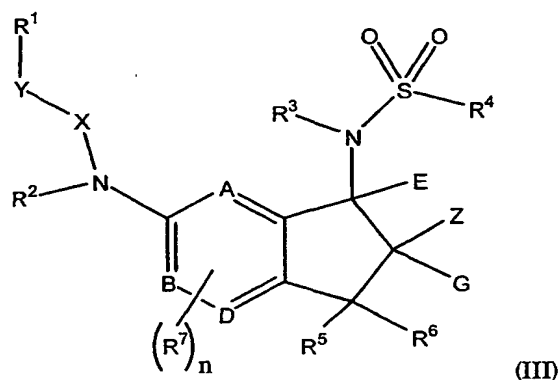
Z is selected from hydrogen, alkyl, hydroxyl, amino and substituted amino;

with the provisos that

i) when R⁴ is aryl, then R⁴ is not a 3,4-dialkoxy phenyl, or a 3-cycloalkylalkoxy, 4-alkoxy phenyl and

ii) when A, B, and D are all CH, and Z is H, OR^a, or NR^bR^c wherein R^a is one of H, (CH₂)_m-R⁸ or C(O)-(CH₂)_m-R⁸, m is 1 to 5, R⁸ is N(R⁹)₂, N(R⁹)₃L or CO₂R⁹, each R⁹ being independently selected from one of H or alkyl, and L is a counter ion, R^b is H or alkyl; R^c is H, alkyl, or CO₂R¹⁰, and R¹⁰ is alkyl; then when R² is hydrogen, or methyl, R³ is not hydrogen, or alkyl, and when R³ is H, or alkyl then R² is not H, or methyl.

3. A compound having potassium channel inhibitory activity of formula (III), or a pharmaceutically acceptable salt or prodrug thereof:



wherein,

A, B, and D are substituted carbon atoms, or one of A, B, and D is a nitrogen atom, or N→O;

E and G are each hydrogen, or E and G taken together form a bond;

R¹ is selected from hydrogen, alkyl, carbocycloalkyl, aryl, heterocyclo, heteroaryl, alkoxy, aryloxy, and substituted amino;

Y is selected from a bond, alkyl, carbocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclo;

X is one of C=O, C=S or SO₂;

R² and R³ are independently selected from hydrogen, alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, (heteroaryl)alkyl, aminoalkyl; substituted aminoalkyl, carboxyalkyl, alkoxyalkanoyl and aminoalkanoyl;

R⁴ is selected from alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heteroaryl and heterocyclo;

R⁵ and R⁶ are each independently selected from hydrogen and alkyl;

R⁷ is independently selected from hydrogen, alkyl, hydroxy, alkoxy, amino, substituted amino, nitro, cyano, halo, carboxy, alkoxycarbonyl, aminocarbonyl, substituted aminocarbonyl and n is 1, 2 or 3;

Z is selected from hydrogen, alkyl, hydroxy, SH, alkoxy, aryloxy, alkylthio, amino, substituted amino, alkoxyalkanoyl, alkanoylamido, aroylamido, heteroaroylamido, heterocyclocarbonylamido, alkanoyl(alkylsubstituted)amido, aroyl(alkylsubstituted)amido, heteroaroyl(alkylsubstituted)amido and heterocyclocarbonyl(alkylsubstituted)amido;

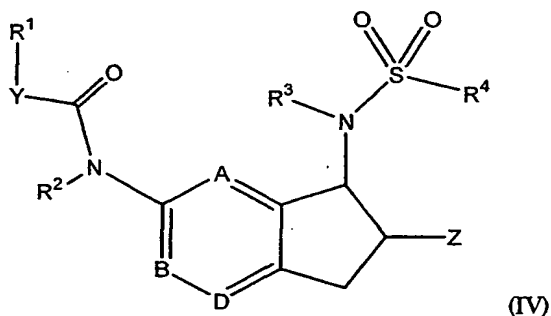
with the provisos that

i) when R⁴ is aryl, then R⁴ is not a 3,4-dialkoxy phenyl, or a 3-cycloalkylalkoxy, 4-alkoxy phenyl and

ii) when A, B, and D are all CH, and Z is H, OR^a, or NR^bR^c wherein R^a is one of H, (CH₂)_m-R⁸ or C(O)-(CH₂)_m-R⁸, m is 1 to 5, R⁸ is N(R⁹)₂, N(R⁹)₃L or CO₂R⁹, each R⁹ being independently selected from one of H or alkyl, and L is a counter ion, R^b is H or

alkyl; R^c is H, alkyl, or CO_2R^{10} , and R^{10} is alkyl; then when R^2 is hydrogen, or methyl, R^3 is not hydrogen, or alkyl, and when R^3 is H, or alkyl then R^2 is not H, or methyl.

4. A compound having potassium channel inhibitory activity of formula (IV), or a pharmaceutically acceptable salt or prodrug thereof:



wherein

A, B, and D are all CH, or one of A, B, and D is a nitrogen atom or $\text{N} \rightarrow \text{O}$;

R^1 is selected from hydrogen, alkyl, carbocycloalkyl, aryl, heterocyclo, heteroaryl, alkoxy, aryloxy and substituted amino;

Y is selected from a bond, alkyl, carbocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclo;

R^2 and R^3 are independently selected from hydrogen, alkyl, carbocycloalkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, (heteroaryl)alkyl, aminoalkyl; substituted aminoalkyl, carboxyalkyl, alkoxyalkanoyl and aminoalkanoyl;

R^4 is selected from aryl, heteroaryl and heterocyclo;

Z is selected from hydrogen, alkyl, hydroxy, SH, alkoxy, aryloxy, alkylthio, amino, substituted amino, alkoxyalkanoyl, alkanoylamido, aroylamido, heteroaroylamido,

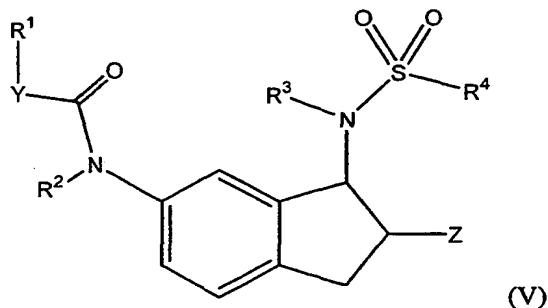
heterocyclocarbonylamido, alkanoyl(alkylsubstituted)amido, aroyl(alkylsubstituted)amido, heteroaroyl(alkylsubstituted)amido and heterocyclocarbonyl(alkylsubstituted)amido;

with the provisos that

i) when R^4 is aryl, then R^4 is not a 3,4-dialkoxy phenyl, or a 3-cycloalkylalkoxy, 4-alkoxy phenyl and

ii) when A, B, and D are all CH, and Z is H, OR^a , or NR^bR^c wherein R^a is one of H, $(CH_2)_m-R^8$ or $C(O)-(CH_2)_m-R^8$, m is 1 to 5, R^8 is $N(R^9)_2$, $N(R^9)_3L$ or CO_2R^9 , each R^9 being independently selected from one of H or alkyl, and L is a counter ion, R^b is H or alkyl; R^c is H, alkyl, or CO_2R^{10} , and R^{10} is alkyl; then when R^2 is hydrogen, or methyl, R^3 is not hydrogen, or alkyl, and when R^3 is H, or alkyl then R^2 is not H, or methyl.

5. A compound having potassium channel inhibitory activity of formula (V), or a pharmaceutically acceptable salt or prodrug thereof:



R^1 is selected from hydrogen, alkyl, carbocycloalkyl, aryl, heterocyclo, heteroaryl, alkoxy, aryloxy and substituted amino;

Y is selected from a single bond, alkyl, carbocycloalkyl, aryl, heteroaryl and heterocyclo;

R^2 is selected from aryl, aralkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl and heteroaralkyl;

R^3 is selected from hydrogen, alkyl, aryl, aralkyl, heteroaryl and heteroaralkyl;

R^4 is selected from aryl, heteroaryl and heterocyclo;

Z is selected from hydrogen and hydroxyl;

with the provisos that when R^4 is aryl, then R^4 is not a 3,4-dialkoxy phenyl, or a 3-cycloalkylalkoxy, 4-alkoxy phenyl.

6. The compound of claim 1, or a pharmaceutically acceptable salt or prodrug thereof, wherein X is C=O.

7. A pharmaceutical composition comprising the compound of claim 1, or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable diluent or carrier.

8. A pharmaceutical composition comprising the compound of claim 2, or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable diluent or carrier.

9. A pharmaceutical composition comprising the compound of claim 3, or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable diluent or carrier.

10. A pharmaceutical composition comprising the compound of claim 4, or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable diluent or carrier.

11. A pharmaceutical composition comprising the compound of claim 5, or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable diluent or carrier.

12. A pharmaceutical composition comprising the compound of claim 6, or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable diluent or carrier.

13. A method for inhibiting potassium transport across cellular membranes possessing potassium channels comprising exposing a cell membrane possessing said channels to the presence of the compound of claim 1, or a pharmaceutically acceptable salt or prodrug thereof.

14. The method of claim 13 wherein the potassium channel is a voltage gated potassium channel.

15. The method of claim 14 wherein the potassium channel is selected from a potassium channel responsible for cardiac I_{Kur} potassium current, a potassium channel responsible for T-lymphocyte I_{Kn} potassium current and potassium channels containing one of Kv1.5 or Kv1.3 α -subunit gene products.

16. A method for inhibiting potassium transport across cellular membranes possessing potassium channels comprising exposing a cell membrane possessing said channels to the presence of the compound of claim 2, or a pharmaceutically acceptable salt or prodrug thereof.

17. The method of claim 16 wherein the potassium channel is a voltage gated potassium channel.

18. The method of claim 17 wherein the potassium channel is selected from a potassium channel responsible for cardiac I_{Kur} potassium current, a potassium channel responsible for T-lymphocyte I_{Kn} potassium current and potassium channels containing one of Kv1.5 or Kv1.3 α -subunit gene products.

19. A method for inhibiting potassium transport across cellular membranes possessing potassium channels comprising exposing a cell membrane possessing said channels to the presence of the compound of claim 3, or a pharmaceutically acceptable salt or prodrug thereof.

20. The method of claim 19 wherein the potassium channel is a voltage gated potassium channel.

21. The method of claim 20 wherein the potassium channel is selected from a potassium channel responsible for cardiac I_{Kur} potassium current, a potassium channel responsible for T-lymphocyte I_{Kn} potassium current and potassium channels containing

one of Kv1.5 or Kv1.3 α -subunit gene products.

22. A method for treating cardiac arrhythmias which comprises administering to a patient in need thereof, a pharmaceutically effective amount of the compound of claim 1, or a pharmaceutically acceptable salt or prodrug thereof.

23. A method for treating a cell proliferative disorder which comprises administering to a patient in need thereof, a pharmaceutically effective amount of the compound of claim 1, or a pharmaceutically acceptable salt or prodrug thereof.

24. A method for treating cardiac arrhythmias which comprises administering to a patient in need thereof, a pharmaceutically effective amount of the compound of claim 2, or a pharmaceutically acceptable salt or prodrug thereof.

25. A method for treating a cell proliferative disorder which comprises administering to a patient in need thereof, a pharmaceutically effective amount of the compound of claim 2, or a pharmaceutically acceptable salt or prodrug thereof.

26. A method for treating cardiac arrhythmias which comprises administering to a patient in need thereof, a pharmaceutically effective amount of the compound of claim 3, or a pharmaceutically acceptable salt or prodrug thereof.

27. A method for treating a cell proliferative disorder which comprises administering to a patient in need thereof, a pharmaceutically effective amount of the compound of claim 3, or a pharmaceutically acceptable salt or prodrug thereof.

28. A method for treating cardiac arrhythmias which comprises administering to a patient in need thereof, a pharmaceutically effective amount of the compound of claim 4, or a pharmaceutically acceptable salt or prodrug thereof.

29. A method for treating cardiac arrhythmias which comprises administering to a patient in need thereof, a pharmaceutically effective amount of the compound of claim 5, or a pharmaceutically acceptable salt or prodrug thereof.

30. A method for treating cardiac arrhythmias which comprises administering to a patient in need thereof, a pharmaceutically effective amount of the compound of claim 6, or a pharmaceutically acceptable salt or prodrug thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/34765

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D233/64 C07D213/38 C07D239/42 C07D213/40 A61K31/44
 A61K31/505 A61K31/415 A61P9/04 A61P9/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 04521 A (CASTLE NEIL ALEXANDER ;HUGHES PHILIP FLOYD (US); WILSON JOSEPH WEN) 5 February 1998 (1998-02-05) cited in the application see claims and examples ----	1-30
Y	WO 99 37607 A (ICAGEN INC) 29 July 1999 (1999-07-29) see definitions of R4 and R3 and Table 1B ----	1-30
Y	EP 0 915 087 A (HOECHST MARION ROUSSEL DE GMBH) 12 May 1999 (1999-05-12) see all of the definitions, especially R5-R8 ----	1-30
P,Y	WO 00 12077 A (SQUIBB BRISTOL MYERS CO) 9 March 2000 (2000-03-09) see definitions of Q ----- -/--	1-30



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

20 March 2001

Date of mailing of the international search report

129.03.01

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Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/34765

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 36596 A (CHIROSCIENCE LTD) 21 November 1996 (1996-11-21) see definitions of R4 -----	1-30

INTERNATIONAL SEARCH REPORT

international application No.
PCT/US 00/34765

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1-30 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 13-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claim 1 states that A,B and D are selected from "substituted" carbon atoms, yet it is apparent that CH is intended to be included (see provisos and subsequent claims), which would not normally fall under the term substituted. The search has been carried out both for CH and substituted carbon.

Continuation of Box I.2

Claims Nos.: 1-30 (partly)

Present claims 1-30 relate to an extremely large number of possible compounds in that the term "preodrug" is included within each claim. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only the actual compounds, not for any theoretical prodrugs thereof. In the present case, the term prodrug so lacks support, and the application in this respect so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the claims other than the prodrugs of the compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/34765

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